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ORIGINAL ARTICLE

Pediatric Multisystemic Inflammatory Syndrome Temporarily associated with COVID-19: clinical characteristics and management in a Pediatric Critical Care Unit

Síndrome Inflamatorio Multisistémico Pediátrico asociado a COVID-19: características clínicas y manejo en una Unidad de Paciente Crítico Pediátrico

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What do we know about the subject matter of this study?

It is a new inflammatory syndrome, temporarily associated with COVID-19, whose pathophysiology is under investigation and that can lead to vital risk. Its differential diagnosis should be early considered in critically ill pediatric patients.

What does this study contribute to what is already known?

It provides a detailed clinical and laboratory description of the severe evolution of patients with this syndrome, establishing a temporality of signs and symptoms that allow early suspicion, as well as the favorable response to a standardized immunomodulatory treatment.

Abstract

In April 2020, the pediatric multisystem inflammatory syndrome temporarily associated with COVID-19 (MIS-C) was described for the first time. MIS-C could have a severe course and may require critical care support. **Objective:** To describe the clinical, laboratory, and management characteristics of hospitalized children who meet MIS-C criteria with severe presentation in a pediatric critical patient unit. **Patients and Method:** Descriptive prospective study of children with severe MIS-C managed by treatment phases with immunoglobulin and methylprednisolone, according to their clinical response. Epidemiological, clinical, laboratory and imaging data were obtained. Phenotypes were classified into Kawasaki and not Kawasaki, comparing their findings. **Results:** 20 patients were analyzed, the median age was 6 years, 60% were female, and 40% presented comorbidity. SARS-CoV-2 was detected in 90% of the patients. They presented fever as the first symptom, followed by brief

Keywords:
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and early gastrointestinal symptoms (70%). 75% presented the Kawasaki phenotype. They evolved with lymphopenia, hypoalbuminemia, coagulation alterations, and elevated systemic and cardiac inflammatory parameters. 80% of the cases presented echocardiographic alterations and 90% shock that required critical care support. All the patients had a short and favorable evolution. All patients responded to the established therapy, but 40% required a second phase of treatment. There were no differences when comparing phenotypes. No deaths were reported. **Conclusion:** MIS-C is a new childhood disease whose presentation could be life-threatening. It requires early suspicion, immunomodulatory management, critical care support, and a multidisciplinary approach to obtain the best results and optimize its prognosis.

Introduction

The burden of disease caused by the new SARS-CoV-2 coronavirus has focused on adults[1,2]. In children, this infection usually manifests as a mild to moderate and even asymptomatic acute respiratory illness, with low hospitalization and mortality rates[3-5].

In April 2020, reports from Italy and the United Kingdom described a multisystem inflammatory syndrome occurring 2 to 6 weeks after SARS-CoV-2 infection in the pediatric population. The disease was named multisystem inflammatory syndrome temporally related to COVID-19 (MIS-C) (). Its diagnostic criteria were published by several health institutions including the World Health Organization (WHO[6-8]. This entity shares common clinical features with other known pediatric syndromes such as Kawasaki disease (KD) and toxic shock syndrome (TSS)[9,10], and it is characterized by fever, gastrointestinal symptoms, KD criteria, hypercoagulability, and laboratory parameters within severe inflammatory range, with or without shock.

In Chile, the first case of COVID-19 was confirmed on March 3, 2020, with a peak of cases in the epidemiological week (EW) 25[11], and as in international series, children were affected to a lesser degree, both in severity and frequency, representing approximately 5% of cases[5]. The first cases of MIS-C in Chile were reported in the EW 23[4], and subsequently diagnostic and management guidelines were developed by the Chilean Society of Infectious Diseases and the Chilean Ministry of Health[12].

The disease has only recently been described and its pathophysiology is not clearly known, but it has been described that it can evolve severely, simulating other severe and life-threatening diseases, which presents a diagnostic and management challenge for critical care teams. The objective of this study was to describe the clinical characteristics and management of patients with severe MIC-C, who required hospitalization in a Pediatric Intensive Care Unit (PICU

Patients and Method

Study design and patients

Prospective descriptive study. All patients admitted to the - *Dr. Exequiel González Cortés children`s hospital* (HEGC) – a pediatric reference hospital in the southern area of Santiago – with a diagnosis of severe MIS-C between June 7 and August 1, 2020(corresponding to EW 24 and 31) were included. Case definition was classified according to WHO criteria[8]. Severity was defined by the need for admission to the PICU due to hemodynamic compromise and/or the need for advanced monitoring. Those patients with MIS-C whose hemodynamic stability did not require admission to the PICU were excluded.

The study was approved by the Investigational Research Board of the HEGC and the Ethics Committee of the Faculty of Medicine of the University of Chile. Informed consent from the parents/guardians of the participating patients was obtained by telephone, followed by digital contact. Information was collected from the electronic clinical records of the HEGC. A coded database was created for registering the information (Microsoft Excel), safeguarding patient confidentiality.

The first 6 patients selected for this study were part of a brief communication by the authors for the chilean Society of Pediatrics[13] and of a pediatric collaborative study[4].

Demographic, clinical, and epidemiological data

Demographic variables such as age, sex, and comorbidities were collected. An etiological study of SARS-CoV-2 was performed by polymerase chain reaction (PCR) from a nasopharyngeal swab sample (Real-Time PCR and Cobas 6800® SARS-CoV-2 test, Roche) and IgM/IgG serology by immunochromatographic assay (Standard Q COVID-19 IgM/IgG Duo test, SD Biosensor). The epidemiological link was determined when there was a history of COVID-19 and/or contact with a family member diagnosed as a confirmed or probable case of COVID-19.

The clinical variables analyzed were fever, gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), clinical signs of KD (rash, mucosal changes, conjunctivitis injection, swollen hands and feet, and lymphadenopathy), neurological symptoms (headache, irritability, and seizures), and respiratory symptoms (cough, rhinorrhea odynophagia, and respiratory insufficiency). Patients were classified according to the clinical spectrum of presentation as Kawasaki phenotype if they had clinical elements for KD, classic or incomplete, according to the American Heart Association (AHA) criteria or as non-Kawasaki phenotype if they did not apply to them[14].

The study, diagnosis, and management were performed in a standardized way to all patients in the study, according to a local multidisciplinary guideline developed by pediatric infectious disease specialists, hematologists, cardiologists, allergist/immunologists, and the critical care team, based on WHO recommendations and other international protocols available at the time of its development[15] (figure 1).

For the analysis of laboratory tests, the worst value obtained during the first 48 hours of hospitalization was used. Cardiac involvement was quantified by creatine kinase (CK) and creatine kinase MB (CK-MB), troponin T, pro-brain natriuretic peptide (proBNP), electrocardiogram (ECG), and/or continuous ECG monitoring, in addition to echocardiography performed by the cardiologist within 24 hours of admission. The following alterations were defined: ventricular dysfunction, pericardial effusion, pulmonary hypertension, valve alteration, and coronary alteration with refringence, dilatation, and/or aneurysm, the latter according to the z score defined by the AHA[14].

Inflammatory variables were measured with C-reactive protein (CRP) test, erythrocyte sedimentation rate (ESR), procalcitonin, ferritin, albumin, and quantification of interleukin 6 (IL-6) in plasma. Hematological assays included complete blood count. Lymphopenia was defined as an absolute lymphocyte count < 1500 per μL. D-dimer (DD), fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were measured as coagulation variables. Biochemical and perfusion variables were obtained by measuring lactic acid, central venous O_2 saturation ($ScvO_2$), venous-to-arterial CO_2 difference [$P(v\text{-}a)CO_2$], renal function (creatinine and urea nitrogen), and liver function (transaminases).

To evaluate the presence of any other infectious focus, blood and urine cultures, direct immunofluorescence and/or PCR for the study of respiratory viruses, and chest X-ray were performed. Other imaging such as abdominal ultrasound and computed tomography scan (CT) were also carried out depending on the patient's need. PICU support was measured by determining the presence of shock according to the Surviving Sepsis Campaign (SSC) guideline[16], the need for mechanical ventilation (MV), and other supportive therapies such as non-invasive MV, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO). Shock management was evaluated according to the need for fluid resuscitation and/or vasoactive, and the vasoactive-inotropic score (VIS)[17]. Pediatric Index of Mortality (PIM-2)[18] was established as a mortality score, and Pediatric logistic organ dysfunction (PELOD) score[19] was used to establish organ dysfunction. Other variables studied were PICU length of stay (LOS) and mortality at discharge and 28 days.

Treatment was defined in 3 progressive phases, depending on the clinical course (figure 1). In phase 1 intravenous immunoglobulin G (IVIG), corticosteroids, and associated empirical antibiotic treatment (ceftriaxone and clindamycin) were administrated. Low-molecular-weight heparin (LMWH) in prophylactic dose was added if the patients presented DD over 1500 ng/ml. Aspirin (ASA) was reserved for patients presenting with Kawasaki phenotype. Refractory to phase 1 was considered if the patient persisted febrile 36 hours after the end of IVIG infusion. In these cases, phase 2 treatment was started, with a second dose of IVIG and a more than 4-fold increase in the dose of corticosteroids. The criteria for refractoriness to phase 2 were the same as those used for phase 1. If the patient remained febrile, a phase 3 was considered, consisting in the use of biologic therapy with infliximab or tocilizumab. Corticosteroids were progressively decreased with prednisone at doses of 2, 1, and 0.5 mg/kg/day for 3 days each. Antibiotics were discontinued when bacterial infection was ruled out. ASA dose was adjusted 48 hours after the cessation of fever to continue with maintenance doses of 3 mg/kg/day. LMWH was discontinued on the seventh day if no thrombotic events occurred.

Statistical Analysis

Due to the descriptive design of the study and the fact that this is a recent pathology, the sample size was not calculated. Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range, IQR), according to normal distribution. To evaluate the difference between groups, the Student T-test was used for variables with normal distribution and the Mann-Whitney U test for those without it. Categorical variables were expressed as frequency (percentage) and Fischer's exact test was used to determine group differences. A p-value < 0.05 was considered a significant difference and the STATA 13 software was used for statistical analysis.

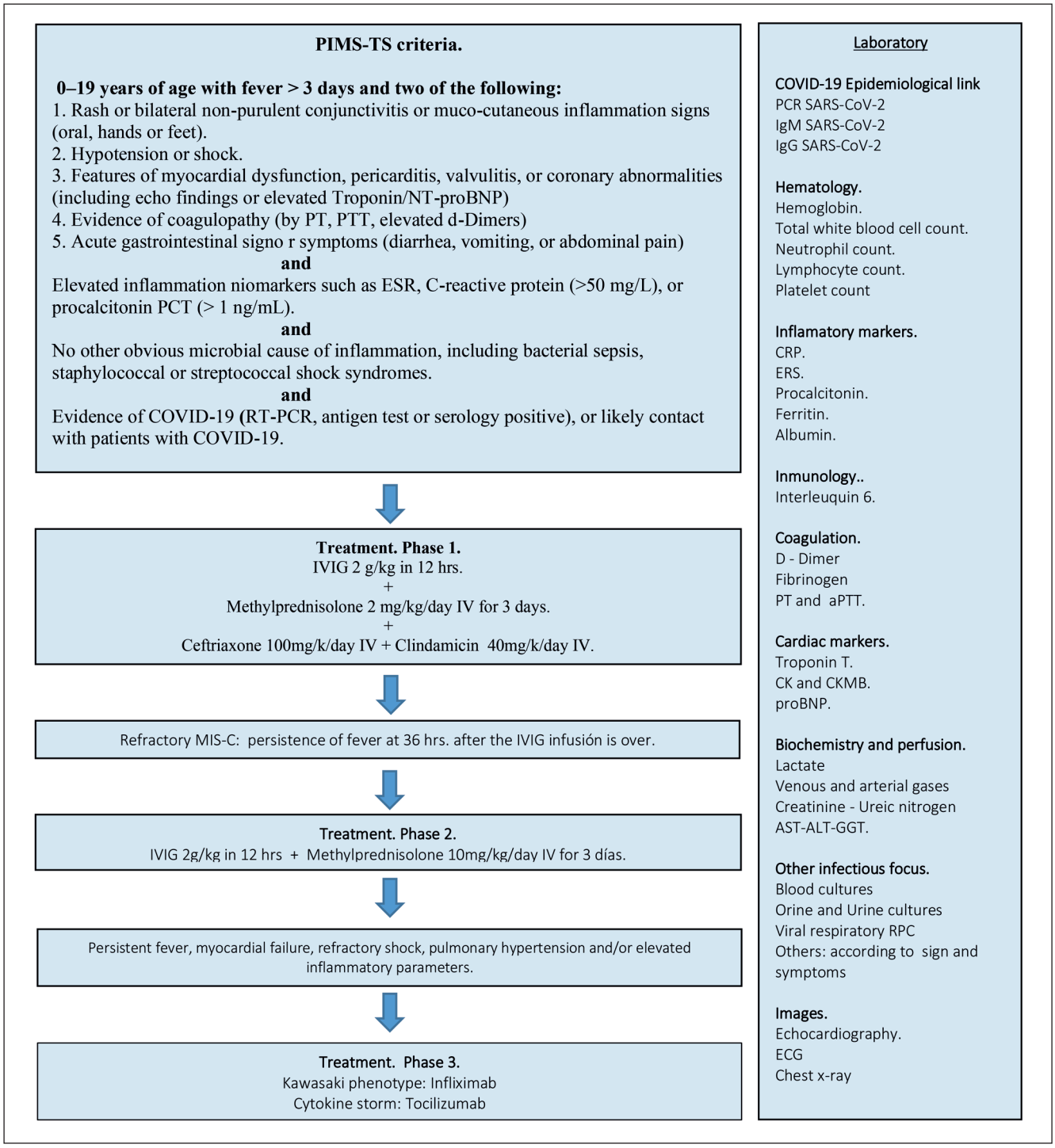

Figure 1. Algorithm for patients with severe MIS-C *.*MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19. PCR: Polymerase chain reaction. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. PT: Prothrombin time. aPTT: Activated partial thromboplastin time. CK: Creatine kinase. CKMB: Creatine kinase-M. proBNP: Brain type natriuretic peptide. BUN: Blood Urea Nitrogen. AST: aspartate aminotransferase.

Results

Demographic, clinical, and epidemiological data

During the study period, 553 patients were admitted to the HEGC, 103 of them due to COVID-19, and 27 of these presented MIS-C. In this period, 122 patients were admitted to PICU, 30 of them due to COVID-19, of whom 20 were diagnosed with severe MIS.C. 74% of all MIS-C patients admitted to the HEGC required supportive therapy at PICU, representing 16%

(20/122) of the total admissions and 67% (20/30) of the COVID-19 in-patient in this unit.

The PRC positivity rate in the southern area of Santiago decreased from 49 to 7% in the EW studied, with a peak of positivity rate of 54% reached in EW 22, according to data obtained from the molecular biology laboratory of the *Hospital Dr. Lucio Córdova*, a reference center for the study of Real-Time PCR for SARS-CoV-2 in the southern area of Santiago (unpublished data). The first cases of MIS-C in the area were reported in EW 24, two weeks after the PCR positivity rate peak and the maximum frequency occurred in EW 28 with 8 cases, of whom 6 - were severe.

The median age was 6 years, 60% of the patients were female. 4% had some comorbidity (table 1). The median hospital and PICU LOS was 9.5 days (IQR: 1 to 12.8) and 5 days (4 to 6) respectively. There were no deaths in our study.

SARS-CoV-2 infection

An association with COVID-19 was evidenced in a 100% of the patients -. The presence of the virus was observed in 90% of the subjects, in 15% SARS-CoV-2 was identified only by real-time PCR, 45% exclusively by serology (IgG, IgM, or both), and 30% had simultaneous positive molecular and serological study con-

Table 1. Demographic, clinical and epidemiological characteristics of patients with severe MIS-C*

Characteristics	Total	Kawasaki phenotype	Non- Kawasaki phenotype
n	20	15	5
Age. median (IQR)	6 (1-7)	4 (1-6)	10 (6-11)
Sex. n (%)			
Female	12 (60)	8	3
Comorbidity. n (%)	8§ (40)	7	2
SARS-CoV-2. n (%)	18 (90)	14	4
PCR (+)	9 (45)	7	2
Serology (+)[a]	15 (75)	12	3
Epidemiological link. n (%)	10 (50)	7	3
COVID-19[b]	1 (5)	1	---
COVID-19 close contact	9 (45)	6	3
Clinical findings. n (%)			
Fever	20 (100)	15	5
Kawasaki Disease sign and symtomps	15 (75)	15	---
Rash	12 (60)	12	---
Mucous membrane changes	10 (50)	10	---
Conjunctival injection	10 (50)	10	---
Swollen hands and feet	8 (40)	8	---
Lymphadenopathy	---	---	---
Gastrointestinal symtpoms	18 (90)	13	5
Abdominal pain	14 (70)	9	5
Diarrhea	9 (45)	5	4
Vomiting	12 (60)	9	3
Respiratory symptoms[1]	3 (15)	2	1
Neurological symptoms[2]	5 (25)	5	0
PICU LOS. Mediana (IQR)	5 (4-6)	5 (4-6)	5 (5-6)
Hospital LOS. Median (IQR)	9 (7-12)	9 (7-13)	10 (8-11)
Mortality at discharge or at 28 days. Median (IQR)	---	---	---

*MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19. IQR: interquartile range. PCR: Polymerase chain reaction. §4 asthmatic, 3 obese and 1allergic rinitis patients. [a]IgM+ and/or IgG +. [b]It includes respiratory sympotms before MIS-C. [1]Cough, rhinorrhea, sore throat and/or respiratorry insufficiency. [2]Headache, irritability and/or seizures. LOS: lenght of stay (days). PICU: Pediatric Intensive Care Unit.

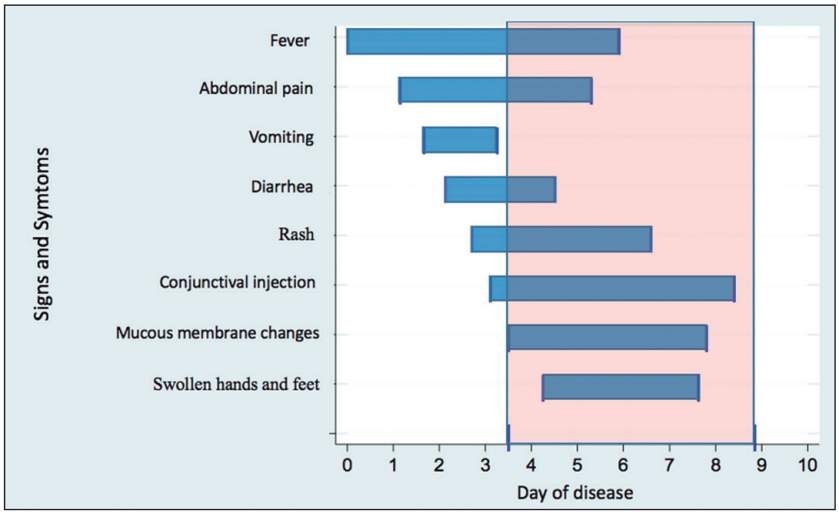

Figure 2. Evolution and duration of symptoms and signs according to days of illness in patients with severe MIS-C*. *MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19. The red area is the PICU lenght of stay. The origin of each blue bar represents the beginning of the symptom, considering as day 0 the disease clinical onset. Duration expresed in averaged-days (standard deviation). Fever: 5.9 (2.2); Abdominal pain: 4.2 (3); Vomiting: 1.6 (0.9); Diarrhea: 2.4 (3.9); Rash: 3.9 (1.9); Conjunctival injection 5.3 (3.5); Mucous membrane changes 4.3 (2.7); Swollen hands and feet: 3.4 (1.8). PICU: pediatric intensive care unit.

firmation. 70% of the patients had positive IgG, 6 of them also had positive IgM. The two patients without viral identification had an epidemiological link.

The epidemiologic link was established in half of the patients, most of them because they were in close contact with a relative with SARS-CoV-2, and only 1 patient presented symptoms of COVID-19 before MIS-C (table 1).

Clinical findings

All patients presented fever-as the first symptom, with onset 3.5 days before hospitalization with an average duration of 5.9 days (SD 2.2). Signs of KD started on day 3 and had an average duration of 5.5 days (SD 2.8). The most frequent sign was exanthema, followed by changes in oral mucosa and non-exudative conjunctivitis. We identified gastrointestinal symptoms in most patients, where abdominal pain was the most frequent. These symptoms were of early onset, with at least one of them occurring 1.4 days from the onset of fever, with a mean duration of 4.4 days (SD 3.4). The Kawasaki phenotype was the most frequent presentation, of which 80% (12 patients) had incomplete KD criteria (table 1). Figure 2 shows the evolution and duration of signs and symptoms over time, starting from the onset of the symptoms and their relationship with the time of hospitalization in the PICU.

Laboratory findings

The parameters measured were compatible with acute inflammation in most patients, with increased CRP, procalcitonin, and ferritin, regardless of the presentation phenotype. Hypoalbuminemia was frequently observed. Hematologic findings were predominantly anemia and lymphopenia. Regarding coagulation parameters, all patients studied had elevated DD and fibrinogen, however, most patients maintained PT and aPTT within normal ranges. 85% (n = 17) of patients presented elevated IL-6, including 2 cases with values > 2000 pg/mL. 95% of patients had cardiac inflammation, measured by troponin T and the same percentage of patients had elevated proBNP, compatible with heart failure.

In the biochemical and perfusion laboratory tests, most patients did not present elevated lactate or altered venous oxygen saturation, and only 5 of them had altered P(v-a) CO_2 values. When comparing the results between Kawasaki and non-Kawasaki phenotypes, there was a trend to more altered values in the latter group, with no statistical significance, except for creatinine and transaminases ($p < 0.05$). No other agent or infectious focus was identified in any patient. Table 2 details the laboratory findings.

Imaging

Six patients were studied with abdominal imaging (3 CT scans and 3 ultrasound) due to acute abdominal symptoms. The most frequent findings were mesenteric adenitis in 4 patients, ileocolitis in 3 patients, hepatomegaly in 3 patients, and splenomegaly in one patient. These findings occurred independently of the clinical phenotype. Altered chest X-ray showed perihilar infiltrate in 5 patients.

Electrocardiographic and echocardiographic findings

The ECG and/or continuous monitoring was altered in one patient, presenting ventricular tachycardia with pulse. 80% of the patients presented an abnormal echocardiogram. Coronary abnormality was the most

Table 2. Laboratory values of patients with severe MIS-C*

Laboratory	Reference value	Total Median (IQR)	Kawasaki phenotype Median (IQR)	Non-Kawasaki phenotype Median (IQR)
Hematology				
Hemoglobin (g/dL).	(10.7-15.6)	8.8 (8.2-9.5)	8.7 (7.6-9.3)	9.5 (8.4-9.9)
White blood cell count (x 1000/μL)	(4.5-13.5)	14.9 (6.9-20.1)	14.2 (6.1-20.1)	18.1 (14.3-20.2)
Neutrophil count (x 1000/μL)	(> 1.5)	8.1 (4.4-10.5)	6.6 (3.0-9.6)	10.9 (8.5-1.2)
Lymphocyte count (x 1000/μL)	(2-10)	0.8 (0.6-1.0)	0.8 (0.6-1.7)	0.8 (0.7-0.9)
Platelet count (x 1000/μL)	(140-450)	165 (113-246)	167 (112-247)	137 (114-246)
Inflammatory markers				
CRP (mg/dL)	(< = 5)	132 (100-344)	127 (47-356)	275 (132-315)
ESR (mm/hr)	(1-20)	49 (28-62)	52 (38-63)	39 (20-54)
Procalcitonin (ng/mL)	(< 0.5)	3.5 (0.6-7.4)	3.1 (0.4-8.2)	5.6 (1.9-6.6)
Ferritin (ng/mL)	(22-322)	228 (162-495)	221 (160-402)	447 (227-542)
Albumin (g/dL)	(3.8-5.4)	2.4 (2.1-2.9)	2.4 (2.1-3.0)	2.3 (2.1-2.5)
Inmunology				
Interleuquin 6 (pg/mL)	(< 3.4)	108 (57-451)	93 (44-365)	153 (69-2.000)
Coagulation				
D-dimer (ng/mL)	(< = 500)	4.524 (3.112-6.069)	4.042 (2.409-5.912)	6.062 (4.520-6.075)
Fibrinogen (mg/dL)	(135-358)	433 (345-597)	416 (314-660)	537 (493-560)
PT (%)	(70-120)	54 (47-65)	60 (46-70)	49 (48-51)
aPTT (seg.)	(25.3-37.9)	33 (30-41)	36 (30-42)	32 (29-32)
Cardiac markers				
Troponin T (ng/dL)	(20-60)	17 (6-38)	16 (7-42)	23 (3-34)
CK (U/L)	(< = 149)	161.0 (88.5-340.5)	187.0 (89-377)	132.0 (52-250)
CK-MB (U/L)	(< = 25)	29.1 (25.8-34.4)	28.0 (24.8-34)	33.0 (30.6-38)
Pro-BNP (pg/mL)	(< 300)	3.790 (1.077-9.350)	3.540 (1.210-10.700)	4.740 (943-8.420)
Biochemistry and perfusion				
Lactate (mg/L)	(4.5-19.8)	17.0 (12.3-22.3)	16.7 (11.7-22)	38.4 (12.5-55)
ScvO2 1 (%)	(> 70%)	70 (62-79)	68 (60-82)	71 (68-75)
CO2 gap 2 (mmHg)	(< 6)	7 (5-9)	8 (5-9)	7 (6-7)
Creatinine (mg/dL)[3]	(0.32-0.87)	0.41 (0.31-0.54)	0.38 (0.3-0.49)	0.56 (0.42-0.75)
BUN (mg/dL)	(5-25)	13 (10-17)	12 (9-16)	16 (14-18)
AST (U/L)[3]	(5-32)	42 (28-67)	37 (27-53)	100 (76-181)
ALT (U/L)[3]	(5-31)	43 (19-57)	39 (17-53)	102 (46-126)
GGT (U/L)[3]	(5-40)	34 (15-70)	21 (13-45)	125 (59-175)

*MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19. IQR: interquartile range. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. PT: Prothrombin time. aPTT: Activated partial thromboplastin time. CK: Creatine kinase. CKMB: Creatine kinase-M. proB-NP: Brain type natriuretic peptide. [1]ScVO2: central venous oxygen saturation. [12]CO2 gap: venous-to-arterial carbon dioxide partial pres- sure difference. BUN: Blood Urea Nitrogen. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gama glutamil transferase. [3]Statistically significant difference between phenotypes ($p < 0.05$).

frequent finding, occurring in 55% of patients (11/20), identifying aneurysms in only 2 of them (10%). Other echocardiographic abnormalities included ventricular dysfunction, pulmonary hypertension, acute valvular heart disease, and pericardial effusion (table 3).

Support at PICU

The subjects-prediction of mortality values upon admission, based on PIM-2 results -were low. Most patients were admitted with shock, requiring fluid resuscitation with crystalloids and -vasoactive support, whose duration was short. The most frequent was the use of epinephrine, which occurred in 16 patients, 12 of whom required association with norepinephrine. No other dysfunctions were observed, except cardiovascular dysfunction, which was compatible with a low PELOD score (Table 4). One of the most used support therapies was invasive MV (IMV), which was initiated

Table 3. Echocardiographic findings in patients with severe MIS-C*

Echocardiographic findings	Total. n = 20	Kawasaki phenotype. n = 15	No Kawasaki phenotype. n = 5
Echocardiographic abnormalities	16 (80%)	13 (87%)	3 (60%)
Ventricular dysfunction	6 (30%)	4 (27%)	2 (40%)
Pericardial effusion	3 (15%)	3 (20%)	----
Pulmonary hypertension	4 (20%)	3 (20%)	1 (20%)
Valve abnormalities	1 (5%)	----	1 (20%)
Coronary abnormalities	11 (55%)	9 (60%)	2 (40%)
Refringence	7 (35%)	5 (33%)	2 (40%)
Dilatation	7 (35%)	6 (40%)	1 (20%)
Aneurysm	2 (10%)	2 (13%)	----

* MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19.

Table 4. Characteristics of intensive support for patients with severe MIS-C*

Characteristics	Total. n = 20	Kawasaki phenotype. n = 15	No Kawasaki phenotype. n = 5
PIM2 (IQR)	1.1 (RIC 0.8-1.3)	1.1 (RIC 0.8-1.2)	1.0 (RIC 0.8-1.4)
Shock (%)	18 (90%)	14 (93%)	4 (80%)
Fluid resuscitation (%)	17 (85%)	13 (87%)	4 (80%)
Total fluid volumen. ml/kg (IQR)	40 (RIC 20-40)	40 (RIC 20-40)	30.0 (RIC 20-55)
Vasoactive support(%)	16 (80%)	12 (80%)	4 (80%)
Days (IQR)	2.0 (RIC 2.0-3.5)	2.0 (RIC 2.0-3.5)	2.5 (RIC 2.0-3.5)
VIS (IQR)	20 (RIC 10-24.8)	15.5 (10-25)	20 (20-23)
Mechanical ventilation			
Invasive (%)		11 (73%)	4 (80%)
VM LOS (IQR)	2 (RIC 2-3)	3 (RIC 2-4)	2 (RIC 2-2)
PELODS (IQR)	12 (RIC 11-12)	11 (RIC 11-12)	12 (RIC 11.5-12)

*MIS-C: Multisystem inflammatory syndrome temporally related to COVID-19. IQR: interquartile range. PIM2: Pediatric Index of Mortality-2. VIS: Vasoactive-inotropic score. VM: Mechanical ventilation. LOS: Length of stay. PELODS: pediatric logistic organ dysfunction score.

due to hemodynamic instability and its duration was limited to the resolution of shock (Table 4). No patient required CRRT or ECMO.

Treatment

100% of the patients analyzed received phase 1 treatment, which started with a median of 17 hours since hospital admission (IQR 11.5 - 18.8). In 60% of the cases, fever ended after phase 1- treatment was established. 40% of subjects were classified as refractory, based on fever persistence criteria, requiring proceed with phase 2 treatment. Remission of fever was achieved in all cases. No patient required phase 3 treatment. We found no differences when comparing demographic, clinical, or laboratory variables according to response to phase of treatment, except for fever persistence.

Discussion

MIS-C is a recently described clinical entity that can be life-threatening in pediatric patients, representing a diagnostic and management challenge, given its similarity to other severe and highly lethal conditions in childhood[16]. The disease begins after the peaks of community infection and hospitalizations due to COVID-19[4,9,20].

In our study, patients with MIS-C presented 6 weeks after the maximum -PRC positivity observed in our area, requiring PICU support and/or advanced monitoring in 74% of cases. This is similar to reports of France and the United States, where intensive management was required in 73 to 80% of the patients[20,21] with a short PICU LOS . On the other hand, 67% of the patients admitted to our PICU due to COVID-19

presented MIS-C, suggesting that this would be the most severe clinical manifestation of SARS-CoV-2 in pediatric age, which would occur more frequently in healthy school children age, with no clinical history of COVID-19, but with some close contact, which was reported in other publications[9,21,22]. In this series, the presentation weeks after SARS-CoV-2 infection would explain the low percentage of molecular diagnosis by nasopharyngeal swab (45%), contrasting with the 93% of IgG positivity.

I In our clinical findings, fever, gastrointestinal symptoms, and signs and symptoms of incomplete KD were important, presented more frequently than in other reports[23-25]. According to the data obtained, our patients were admitted to the PICU with fever, abdominal pain, and diarrhea. Patients with Kawasaki phenotype were also admitted with exanthema and non-exudative conjunctivitis, presenting oral mucosal involvement and edema during hospitalization. This clinical temporality is highly relevant for the management of the disease, considering that fever and gastrointestinal symptoms are the first symptoms and can evolve in a few days to clinical KD with shock, requiring intensive support, which would occur around day 3 of the clinical course.

The laboratory was characterized by systemic inflammation with anemia, lymphopenia, CRP and procalcitonin at levels described in bacterial infections[26,27], high ferritin values, and hypoalbuminemia similar to those reported in other series of patients with MIS-C, which means that the differential diagnosis of severe systemic inflammatory/infectious conditions should consider MIS-C among its probable causes[4,25,28,29].

The hypercoagulable state described in adult and pediatric patients with SARS-CoV-2 infection30,31 is not consistent with the low fibrinogen values usually observed in patients with coagulopathies secondary to septic shock[32]. Our series showed high DD value, in addition to an elevation of fibrinogen, but it was not correlated with evidence of thrombotic phenomena.

Cardiological findings showed cardiac inflammation through biochemical markers, such as troponin T and proBNP. However, they do not agree with the 30% of ventricular dysfunction found by ultrasound, which differs among reports[21,33,34] and should be analyzed in further studies. Our patients presented early coronary alteration, within 24 hours of admission, regardless of Kawasaki or non-Kawasaki phenotype, and the proportion of patients with dilatation or aneurysms (35% and 10%, respectively) was higher than usually reported in KD[14]. This raises the possibility of pathophysiology that could be different from KD or the adult population with cardiac involvement due to COVID-19[3,35,36].

The severity of the clinical presentation of our patients was mostly evidenced by hypotensive shock unresponsive to fluid resuscitation, IMV support, and the use of vasoactive, even more frequently than in other clinical series[37]. However, its rapid and favorable evolution differed from other conditions of similar presentation, such as bacterial septic shock, with fewer PICU LOS , less organ dysfunction according to PELOD score, short time using support therapies, and absence of other advanced support therapies, such as CRRT or ECMO.

The prediction of mortality measured by scores (PIM-2, PELOD, and VIS) was low, consistent with the absence of deceased patients in our study, which is similar to other reports already published[4,38,39] but contrary to reports describing high mortality, even higher than 18%[40].

At the beginning of this study, there were no national guidelines for the management of these patients, so it was decided to manage all cases of severe MIS-C with immunomodulatory therapy associated with IVIG and corticosteroids, based on international reports. A high percentage of the patients in the study continued with fever despite the use of associated therapy, requiring a new dose of IVIG and an increase of more than four times the initial dose of corticosteroids for fever resolution. This findings leads us to consider the administration of methylprednisolone at 10mg/kg/day dose on admission of all patients with severe MIS-C, and which could eventually shorten the duration of the disease. In international protocols, biological therapy was described as a therapeutic alternative[15], however, our results indicate that patients with severe MIS-C did not require it to achieve lower inflammatory parameters, and the ended of both fever and intensive support therapy.

Our study has limitations. The low number of patients, which does not allow us to establish associations between the variables studied, and the absence of subjects aged between 15 and 19 years, so we do not know the frequency and forms of presentation and/or clinical evolution in this group. However, performing a multidisciplinary and collaborative protocol before the peak of admissions due to MIS-C, allowed us to systematize the case management obtain laboratory tests results, and provide a standardized treatment to all patients, in order to compare our results, reducing the bias associated with the different possible therapies to be implemented. We believe that is highly relevant to continue with MIS-C multicenter critical trials, in order to offer therapies validated by scientific data, that can optimize the outcomes and safety in their implementation, for all our patients.

Conclusion

PIMS-TS is a post-infectious clinical manifestation of SARS-CoV-2 that can be life-threatening in pediatric patients. The severe disease presents with gastrointestinal symptoms, evolving with signs of KD, severe inflammatory parameters, and hemodynamic compromise, requiring MV and vasoactive support. It should be suspected early in children with shock who are admitted to a PICU, in order to establish the respective support measures and immunomodulatory therapy, to which they respond rapidly. The multidisciplinary, collaborative, and coordinated approach is essential for its management, monitoring, and long-term follow-up, therefore we can improve the knowledge of this new syndromic entity in pediatrics.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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