



Post-COVID-19 multisystem inflammatory syndrome in children: a case report

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Abstract

Objective: Report of a case of Multisystem Inflammatory Syndrome in Children (MIS-C) post-COVID 19 and review of articles on the topic. **Results:** Coronavirus 2 (SARS-CoV-2) infection is a disease whose symptoms are similar between the adult and pediatric population, ranging from asymptomatic cases to more serious conditions that have spread global terror due to the high number of infections worldwide deaths. However, children have presented a milder clinic. It is worth mentioning, however, that this population is not completely risk-free, with reports of the association of the Coronavirus triggering inflammatory diseases, such as the so-called MIS-C whose complications can be as serious as the forms of symptoms experienced by adults. **Conclusion:** The temporal and serological relationship of a link with SARS-CoV-2 infection is supported by consistent data, however further studies are needed to establish SARS-CoV-2 as an inciting agent. Due to the severity of MIS-C, knowledge about this disease is necessary for a quick diagnosis and early treatment, aiming to reduce systemic lesions. Due to the increase in the number of cases of children affected by MIS-C, the use of immunomodulatory drugs, such as intravenous immunoglobulin (IVIG), aspirin, and systemic glucocorticoids, has been instituted as first-line therapy, to reduce inflammation and late complications.

Keywords: COVID-19. SARS-CoV-2. Systemic Inflammatory Syndrome. Pediatrics. Kawasaki disease.

Introduction

The great impact caused by the disease

Coronavirus has been one of the main challenges to global health in recent years. Despite being dated as recent, this virus was reported more than 60 years ago, and during this period it presented several genetic variabilities [1]. However, the new Coronavirus responsible for social isolation and terror in the population was first identified in China at the end of 2019, being named by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses, of Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. This pathology has affected thousands of individuals, ranging from asymptomatic to symptomatic patients who can progress to severe conditions or even death [3]. Severity is correlated with several risk factors, including comorbidities, such as respiratory and heart diseases and older age [4].

The symptoms of this pathology are similar to the flu (influenza), with fever, chills, prostration, and dry cough and can also cause diarrhea, vomiting, and various types of skin rashes and conjunctivitis, in addition to the involvement of the Central Nervous System and myocarditis in more severe cases [5]. As for adults and the elderly, the disease is similar to the pediatric population, ranging from patients with no clinical manifestation of the disease to more severe cases [6]. However, this population has a milder clinical condition [2]. Part of this is due to the better innate immune response presented by children, in addition to the difference in density of the angiotensin-converting enzyme 2 (ACE2) receptor, compared to adults. ACE2 is a mediator for SARS-Cov-2 entry into cells [7].

It is worth mentioning, however, that this population is not completely risk-free, with reports of the association of the Coronavirus triggering

inflammatory diseases, for example, the similarity with Kawasaki Disease (KD), incomplete KD, and/or toxic shock syndrome [8]. The first evidence of this correlation appeared in Europe and North America in late April 2020 [9]. According to the World Health Organization (WHO), not all symptoms are similar between KD and Coronavirus, so they created a new nomenclature for such an association, the so-called multisystem inflammatory syndrome in children (MIS-C) [5, 10].

The difference exists, as MIS-C affects the gastrointestinal and cardiovascular system more intensely than KD. In addition, despite having fever and mucocutaneous alterations, Multisystem Inflammatory Syndrome affects adolescents and children over 5 years of age, with encephalopathies, myalgia, and respiratory difficulty, which is not common in KD [11,12]. In this sense, Kawasaki disease is considered a vasculitis of unknown etiology, which mainly affects the coronary arteries, targeting children under 5 years of age, with a mean age of onset of 9 to 11 months [13,14]. In the laboratory results, a considerable difference in interleukin 6 (IL-6), interleukin 8 (IL-8), and CRP was noted in MIS-C compared to KD [9]. The MIS-C also had thrombocytopenia, neutrophilia, and lymphopenia; while in KD we have thrombocytosis and neutrophilia [11].

Therefore, the present study reported the evolution of a case of MIS-C and its treatment in a 3-year-old and 5-month-old child affected by MIS-C after SARS-CoV-2, comparing the presented picture with the findings in the literature. to strengthen the data that has been evidenced about the syndrome so far.

Methods

Study Design

The present study was elaborated according to the rules of the CARE case report (<https://www.care-statement.org/>). The descriptors used were “*COVID-19; Kawasaki Disease; SARS-CoV-2; Multisystem Inflammatory Syndrome*”. The most relevant works to the proposed theme were selected, excluding those that did not contemplate the objective of this study. The research was carried out to the Google academic, Scielo, PubMed, and in scientific repositories.

Ethical Approval

This study was analyzed and approved by the Research Ethics Committee from University of Marília, Faculty of Medicine, Marília, Sao Paulo, Brazil, and obtaining the Informed Consent Form according to CNS/CONEP Resolution 466/12.

Informed Consent

Data from the child under study were obtained through the collection and analysis of information contained in the patient's medical record, duly authorized by those responsible using signing the Informed Consent Form, at Santa Casa de Misericórdia Hospital from Marília, where the child was hospitalized in the hospital pediatric Intensive Care Unit (ICU).

Case report

Patient Information and Clinical Findings, Timeline, Diagnostic Assessment, Therapeutic Intervention, and Follow-up

C.D.S.A, a male child aged 3 years and 5 months, born on 05/07/2017, was admitted to Hospital Santa Casa de Misericórdia de Marília on 10/06/2020 with a complaint of difficult-to-control fever with 5 days of evolution, ranging from 38 to 39 °C, in addition to spots distributed throughout the body that appeared after the start of antibiotic administration (amoxicillin associated with clavulanate), which was prescribed considering the initial diagnostic hypothesis of oral lesions by Coxsackievirus with a secondary bacterial infection. The aforementioned medication was prescribed in previous medical care at another health service.

Due to the appearance of the reported rash, it was treated as an allergic reaction (pharmacodermia) to the antibiotic. He also had hypoxia and low fluid intake, in addition to being prostrate. The physical examination showed a child in a regular general condition, edematous, hypoactive, with strong pulses without hemodynamic compromise, having rapid capillary perfusion in 2 seconds, and warm extremities. The patient weight was 12.5 kg. The respiratory rate at the time of admission was 44 breaths per minute, and breath sounds were heard without abnormalities, discomfort in breathing, and dyspnea.

Cardiac auscultation showed rhythmic sounds without murmurs and a heart rate of 170 heartbeats per minute. Abdominal examination with decreased air-fluid sounds on auscultation and hypertympanism on digital percussion of the entire abdomen. There were hyperemic macules on the entire face and some on the trunk and lower limbs. Historically, it was a healthy child, without previous comorbidities and drug and food allergies.

In the anamnesis synthesis, the death of the maternal grandmother by COVID-19 was reported on 09/11/2020 and her maternal grandfather also acquired the infection, but the latter remained oligosymptomatic during the period of infection, with no need for

hospitalization. He was in isolation until 22/09/2020. The child's mother performed an RT-PCR (Polymerase Chain Reaction - reverse transcriptase) test for Coronavirus 2 (SARS-CoV-2) which was negative. The child was transferred from the emergency room to a bed in the Pediatric ICU due to suspicion at this time of Kawasaki Disease (KD) or MIS-C.

On admission (10/06/2020) the following tests were collected with the respective results: Blood count - hemoglobin: 10.9, hematocrit: 31.6, leukocytes: 7,280, with 15% of rods, 67% of segmented, 4% eosinophils, 10% lymphocytes, 4% monocytes, with presence of fine toxic granules in neutrophils, platelets: 97,000, C-reactive protein: 129.76, erythrocyte sedimentation rate: 24, urea: 28, creatinine: 0.42, sodium: 135, potassium: 3.5, total calcium: 7.8, magnesium: 1.8, phosphorus: 3.0, normal transaminases, triglycerides: 214, total cholesterol: 82, lactate: 15.5, activity time prothrombin time: 13.6 sec,

INR: 1.17, prothrombin activity: 76%, activated partial thromboplastin time: 36.6 sec, fibrinogen: 282, total proteins: 3.29, albumin: 2.49, globulin : 1.43, lactic dehydrogenase (LD): 298, ultrasensitive troponin: 0.012, ferritin: 331.5, Anti-streptolysin O: 7.0, D-dimers: 3,900, complements C3: 70 and C4:27, arterial blood gases : pH: 7.27 p CO2: 34.5 pO2: 139.2 bicarbonate:15.5 total CO2: 16.5 Be: -10.5 O2 saturation: 98.5%.

Serologies were collected for cytomegalovirus: IgM: 0.17 (non-reactive), for infectious mononucleosis: heterophile antibodies: non-reactive and IgG for Epstein Barr: 0.03 (non-reactive), for dengue IgM and non-reactive IgG. Blood cultures (2 samples) were collected from different sites: negative, and urine culture: negative. Nasopharyngeal sample collection was also performed for COVID-19 RT-PCR examination. Evolutionary exams during hospitalization are shown in **Table 1**.

Table 1. Evolutionary result of laboratory tests. Legends: (t): total, (i): ionized, (v): venous. The picture shows evolutionary improvement in thrombocytopenia and acute-phase inflammatory protein (C-Reactive Protein), to a decrease in a D-Dimer compared to the value at admission.

Variables/Date	06/10	07/10	08/10	09/10	14/10	15/10	16/10
Hemoglobin	10.9	9.5	7.7	9.8	6.2	7.3	9.6
Hematocrit	31.6	26.6	21.6	29.4	19.2	22.3	28.5
Leukocytes	7.280	7.840	6.300	9.610	21.870		
Rods	15%	00%	01%	01%	02%		
Segmented	67%	63%	60%	85%	46%		
Eosinophils	04%	02%	01%	00%	01%		
Basophiles	00%	00%	01%	00%	01%		
Lymphocytes	10%	32%	33%	08%	36%		
Monocytes	04%	03%	04%	06%	14%		
Platelets	97.000	71.000	85.000	163.000	529.000		
PCR	129.76	111.55			7.92		
Sodium	135	135	134	134	137		
Potassium	3.5	4.0	3.8	4.8	4.5		5.8
Calcium	7.8(t)	5.11(i)		4.99(i)	4.98(i)		
Magnesium	1.8	1.7	1.6	1.8	1.8		
Phosphor	3.0	2.6	3.0	3.8	4.3		
Urea	28	12			25		
Creatinine	0.42	0.33			0.23		
ALT	33						
AST	38						
CKMB	30						
pH	7.27	7.44	7.34	7.40	7.32		
pCO₂	34.5	13.5	44.4	41.4	49.6		
pO₂	139.2	149.5	34.1(v)	47.7(v)	83.1(v)		
Bicarbonate	15.5	8.9	23.5	25.0	25.2		
CO2Total	16.5	9.4	24.9	26.3	26.6		
Be	-10.5	-11.6	-2.2	0.1	-1.6		
Sat O₂	98.5%	99.1%	61.8%	83.5%	95.3%		

Chest radiography showed no abnormalities and chest tomography with a report of normality as well. Abdominal radiography showed global distension of intestinal loops, with edema of the loop wall and the

presence of small amounts of feces in the sigmoid. Cerebrospinal fluid (CSF) was not collected due to the presence of thrombocytopenia and the risk of bleeding from the Central Nervous System (CNS).

After admission, he was medicated with Ceftriaxone 100 mg/kg/day 12/12 hours, Azithromycin 10 mg/kg once a day, Immunoglobulin 2g/kg in 48 hours, Dipyron 25 mg/kg, Paracetamol 10 mg/kg, Midazolam 0.3 mg/kg, Fentanyl 1 mcg/kg, Ketamine 2 mg/kg and 0.9% Physiological Serum 20 ml/Kg. Other measures adopted were fasting and contact and aerosol precautions.

On 10/07/2020, a rapid test for COVID-19 (total antibodies) was carried out, which showed a positive result. The echocardiogram, also performed on that day, showed mild mitral regurgitation, mild left ventricular systolic dysfunction, and pericardial effusion. On that date, antibiotic therapy was also started with Clindamycin at a dose of 40 mg/kg/day intravenously for 6/6h.

On 10/08/2020, serology was collected for COVID-19 (SARS-CoV-2): IgM: 0.30 (non-reactive) and IgG: 6.24 (positive). On that date, the patient was more stable from the respiratory and hemodynamic point of view, but he was anemic and there was a need for blood transfusion. There was an improvement in thrombocytopenia. ASA 5 mg/kg/day was started, with an indication to discontinue if platelets were below 80,000 uL, and vasoactive drugs were replaced by Milrinone, due to increased BP. The dose of this drug needed to be increased and was increased to 0.7 mcg/kg/min on 10/09/2020 due to low venous saturation and signs of cardiac dysfunction reported on the echocardiogram.

After this dose change, there was an improvement and the patient remained hemodynamically stable. Weaning from this drug began on 10/11/2020 and, on 10/12/2020, Captopril 0.5 mg/kg/dose every 8 hours was introduced, which was introduced only when Milrinone was being administered at low doses, close to 0.25 mcg/kg/min. On 10/13/2020, the patient had stable BP without using Milrinone and using Captopril. There was an improvement in the general condition. The echocardiogram was repeated and it showed preserved left and right ventricular systolic function and pericardial effusion.

On 10/14/2020 the patient was stable from a respiratory and hemodynamic point of view and had anemia at the transfusion level, which was performed. The patient was also using Methylprednisolone 2 mg/kg/day and Enoxaparin 10 mg/dose 12/12h until then. These drugs were suspended on this date due to the guidance of hematology, as well as the suspension of antibiotics (Ceftriaxone, Azithromycin, and Clindamycin) because the requested cultures were negative. The result of the RT-PCR COVID-19

performed on 10/6/2020 was negative. A second COVID-19 RT-PCR was performed on 10/09/2020. This second sample also tested negative on 10/14/2020, and contact and aerosol isolation precautions were suspended from that date.

On 10/15/2020 the patient remained hemodynamically stable. Examinations were repeated after the blood transfusion, showing improvement, but still anemic. Blood transfusion was repeated. During the hospitalization period, the patient also used Omeprazole 1.6 mg/kg/intravenous dose due to gastric bleeding, which was the possible cause of persistent anemia. The patient showed laboratory improvement over the length of the hospital stay and remained afebrile throughout this period. With previous diagnoses of COVID-19, MIS-C left ventricular systolic dysfunction with cardiogenic shock, anemia, thrombocytopenia, hydroelectrolyte imbalances and all these having been treated, the patient evolved well and was discharged from the ICU.

Discussion

Based on the articles researched and the case report of the present study, the association between COVID-19 and MIS-C is remarkable. This syndrome can present at any time, but usually occurs 1 to 6 weeks after an infection or may appear superimposed on SARS-CoV-19, suggesting that this inflammation may be a late complication characterized by a disproportionate immune response to the infection [14].

The suspicion of the correlation between COVID-19 and MIS-C, according to the WHO, arises in children under the age of 10 years; fever lasting 3 days or more; in addition to the presence of two or more of the following symptoms: (a) rash or bilateral non-purulent conjunctivitis or signs of mucocutaneous inflammation, (b) hypotension or shock, (c) features of cardiovascular dysfunction, (d) coagulopathy, (e) diarrhea, vomiting or abdominal pain and elevated inflammatory markers [11,12].

It is important to emphasize that for such an association, the diagnosis of COVID-19 alone must be obtained, which is a challenge in the pediatric population. Large epidemiological studies have revealed that the pediatric population represents less than 2% of the total confirmed COVID-19 cases, of which the majority are not serious [7]. The identification of infection by clinical means in children is based on epidemiological criteria and the presence of two or more symptoms of the disease. Regarding the epidemiological criteria, for example, contact with people infected with the virus or with travelers at least 14 days before the onset of symptoms [15]. While the most common

clinical signs in children are fever and cough, abdominal pain, diarrhea, nausea, myalgia, dyspnea, and headache may also occur [6]. Renal, cutaneous, olfactory, gustatory, neurological, and ocular involvement are rare [12].

The severe form of the disease in the pediatric population is rare, however, when present, they are strongly related to MIS-C, with clinical features similar to those of KD, KD shock syndrome, and macrophage activation syndrome (MAS) [11,12]. In addition to the clinical criteria, laboratory diagnosis is also necessary, which has as the gold standard the reverse transcriptase reaction followed by the polymerase chain reaction (RT-PCR), with oropharyngeal or nasal sample collection. Other approaches include diagnostic imaging, such as chest radiography and computed tomography, which aid in diagnosis [16]. It is noteworthy that children are more likely to co-infection with other respiratory viruses and bacteria, and should receive double attention in confirmed cases of COVID-19 associated with respiratory distress [17].

In this sense, a study carried out in the USA showed that all patients with MIS-C had a fever; more than half had exanthema, abdominal pain, and diarrhea, and respiratory manifestations were rare. In most cases, there was a need for admission to intensive care units (ICU), mechanical ventilation, and hemodynamic support [18]. Therefore, in the presence of a child with MIS-C, several tests should be performed to verify the hypercoagulable state, the inflammatory state, and if there was any involvement of organs. Some initial tests are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), to assess inflammatory activity; complete blood count; urea and creatinine for assessment of renal function, and, finally, assessment of liver function and bile ducts [11,12]. After confirmation of MIS-C, follow-up should be supported with other tests, namely: ferritin, triglycerides, HDL, CK, D-dimer, cardiovascular evaluation with electrocardiogram, echocardiogram, and myocardial function markers (troponin, CK-MB, myoglobin, pro-BNP) [11,12].

However, when it is not a positive case for SARS-CoV-2, other differential diagnoses should be taken into account, requiring other complementary tests [6]. Some examples of tests to rule out other infectious causes are stool culture, urine culture, and EAS, ASLO, oropharyngeal culture, blood culture, serology for other possible infections, and lumbar puncture for CSF evaluation when there are signs of central nervous system involvement [11,12].

Considering that the pediatric population can present a rapid evolution to severe forms of the disease,

it is advisable to start treatment as early as possible, which will help to reduce the systemic inflammatory state and restore the proper functioning of organs and systems, minimizing sequelae and mortality associated with these cases. After evaluating the clinical picture and the severity of the patient's condition, individualized treatment should be adopted, with the following interventions being evaluated in each case [10].

Besides, empirical antibiotic therapy needs to be initiated in the presence of shock and/or signs of sepsis, with Ceftriaxone associated with Clindamycin being the most frequently used choice. In cases with moderate and severe manifestations and in those who meet the partial or complete criteria for KD, consideration should be given to the use of intravenous immunoglobulin (IVIG), at a dose of 1-2 g/kg, in a continuous intravenous infusion of 12 hours, with repetition possible in cases refractory to the first dose. In severe presentations and in cases that are refractory to the first dose, it is necessary to consider the use of corticosteroids in association with IVIG. The corticosteroid of choice is Methylprednisolone in the form of pulse therapy, its initial dose ranges from 10 to 30 mg/kg/day for 1 to 3 days, followed by maintenance doses of 2 mg/kg/day for 5 days, after this period is recommended whether to taper doses over the next 2 to 3 weeks.

Also, studies indicate that patients with COVID-19 are at risk of developing thrombotic events, due to their hypercoagulable state, so the use of anticoagulants has to be evaluated individually, taking into account the risk of bleeding [16-18]. Acetylsalicylic acid (ASS) should be used in patients with manifestations of Kawasaki syndrome and/or thrombocytosis ($>450,000/\mu\text{L}$), at a dosage of 30 to 50 mg/kg/day, after cessation of fever for 48 hours, reducing the dose to 3 to 5 mg/kg/day and maintain it until platelet normalization and confirmation of the absence of coronary changes. Inotropic support may be necessary, given the occurrence of ventricular dysfunction and cardiogenic shock in more than 50% of the patients in the study. In cases where there are signs of low systemic output or heart failure with ventricular dysfunction and adequate systemic blood pressure, the inotropes Dobutamine or Milrinone are indicated, whereas in cases where arterial hypotension occurs, Epinephrine in continuous infusion becomes the drug of choice [18].

Still, in some specific cases, the use of immunomodulators is recommended (anti-IL-1, anti-IL-6, or anti-TNF), but so far their benefits and risks have not been adequately elucidated and, therefore, reserved only for cases refractory to two doses of IVIG and pulse

therapy with Methylprednisolone, in which it is believed that exacerbated release of cytokines is occurring [17].

In this context, children were relatively spared from a severe illness in the SARS-CoV-2 pandemic, mainly due to differences in their immune response to the virus, including a lower predisposition to pro-inflammatory states, fewer comorbidities, and differential ACE2 expression [7]. However, there are increasing reports of the development of post-COVID-19 MIS-C. Although a small proportion of children infected with SARS-CoV-2 later develop symptoms of MIS-C, most of them require intensive medical treatment due to the severity of the disease, requiring care in a pediatric intensive care unit [8,13].

Despite the great similarity presented with KD, a differential diagnosis of great importance, some distinctions were evidenced when compared in terms of diagnostic criteria; prevalent clinical presentation, with gastrointestinal symptoms as one of the main manifestations; distribution of mean age in children, who are older; and alterations in laboratory tests, such as the increase in certain cytokines and cellular patterns presented in each of them [9,10]. Due to the increase in the number of cases of children affected by MIS-C, the use of immunomodulatory drugs, such as intravenous immunoglobulin, aspirin, and systemic glucocorticoids, has been instituted as first-line therapy so far, to reduce inflammation and late complications [11].

Due to the severity of MIS-C, knowledge about this disease is necessary for a rapid diagnosis and early treatment, aiming to reduce systemic lesions. Despite presenting mechanisms common to other pathologies, some points still need to be clarified regarding the pathogenesis, the immune response, its long-term consequences, and the possible prevention of this clinical condition [7]. Therefore, understanding the nature of virus-host interactions, and particularly which features of the pediatric immune system facilitate protection or delayed multisystem inflammation, will help to better understand the pathogenesis of SARS-CoV-2, leading to needed improvements in options therapeutics. Furthermore, the temporal and serological plausibility of a link to SARS-CoV-2 infection is supported by consistent data, but further studies are needed to establish SARS-CoV-2 as an inciting agent.

Conclusion

It was concluded that the temporal and serological relationship of a link with SARS-CoV-2 infection is supported by consistent data, however further studies

are needed to establish SARS-CoV-2 as an inciting agent. Due to the severity of MIS-C, knowledge about this disease is necessary for a quick diagnosis and early treatment, aiming to reduce systemic lesions. Due to the increase in the number of cases of children affected by MIS-C, the use of immunomodulatory drugs, such as intravenous immunoglobulin, aspirin, and systemic glucocorticoids, has been instituted as first-line therapy, to reduce inflammation and late complications.

Acknowledgement

Not applicable.

Ethics approval

This study was analyzed and approved by the Research Ethics Committee from University of Marilia, Faculty of Medicine, Marilia, Sao Paulo, Brazil, and obtaining the Informed Consent Form according to CNS/CONEP Resolution 466/12.

Informed consent

The patient signed the consent form.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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