Case Report

Case Report: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 with Coronary Involvement

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Abstract

In the face of the emergence of COVID-19, the multisystem inflammatory syndrome in children (MIS-C), associated with SARS-CoV-2, has shown an increase of cases worldwide among the pediatric population, with clinical presentation and evolution similar to Kawasaki disease. Despite the similarities, these cases present clinical and laboratory particularities that make it necessary to increase the description of similar cases around the world, in order to reach a consensus on this new disease in the future. Here, we bring a Brazilian case, followed up in the countryside of Minas Gerais, in which a cardiovascular involvement was found but with a benign evolution.

Keywords: MIS-C; PIMS-TS; SARS-CoV-2; Kawasaki-like; Coronary dilation

Introduction

Beginning in China on December 19th, the coronavirus 2 (SARS-CoV-2) [1], which, at that time, had not yet been identified in human beings, spread quickly around the world. Although the infection (COVID-19) manifests in adult populations with severe acute interstitial pneumonia, according to
a study conducted in China [2-3] on children under 18 years old, in 29% of the symptomatic cases, this evolution occurred in only 1.7% of cases in the USA. This, in addition to the involvement of the respiratory system showing a more benign evolution [4-5]. However, there are reports of frequent gastrointestinal involvement [6] and, among other symptoms, an incidence increase of Kawasaki or Kawasaki-like syndrome, when associated with SARS-CoV-2 [7-8]—although the acceptance of this terminology is not unanimous.

The first case report of a six-month-old child with Kawasaki disease (DK) and COVID-19 was published in the US on April 7, 2020. At the end of that month, the UK’s National Health Service (NHS) published a warning about children manifesting Kawasaki syndrome and toxic shock syndrome. Meanwhile, studies and case reports began to emerge around the world, corroborating the alert [7]. Published shortly afterwards, an expressive paper presented an observational cohort carried out in Bergamo, Italy, which compared two groups that manifested Kawasaki disease, sorted by period and surveillance for SARS-CoV-2, showed a 30% increase in the incidence of the SARS-CoV-2 group [8].

In the same month, another study conducted in France contained a sample of 21 patients identified with a multisystemic inflammatory syndrome, with clinical and laboratory characteristics similar to Kawasaki’s disease, toxic shock syndrome and macrophage activation syndrome; this was reflected in other later studies as well [8-11]. The reported cases occurred shortly after exposure to COVID-19 (days or weeks), suggesting a possible temporal correlation with SARS-CoV-2 infection, as some patients had positive polymerase chain reaction (PCR) or serology. This syndrome was dubbed the “pediatric multisystemic inflammatory syndrome (MIS-C)”, temporarily associated with SARS-CoV-2, or PIMS-TS [7-12]. Three variations of the disease patterns were reported: a group of children with persistent fever and significant increase in evidence of inflammatory activity, without criteria for Kawasaki disease, shock or organ failure, a second group with Kawasaki disease criteria, and a third group with severe cardiac dysfunction, shock, coronary aneurysms, among other manifestations, including fever and gastrointestinal symptoms [12].

Classic Kawasaki disease is defined as an acute and self-limited vasculitis which affects medium-sized vessels, occurring almost exclusively in children under five years old, with a peak from nine to 11 months [13-14]. Unlike this classic age group, MIS-C temporarily associated with SARS-CoV-2 affected children of an older age group, both indicated in smaller sample studies, as in the UK study with 58 children who developed MIS-C associated with SARS-CoV-2, with an average age of nine years; in an Italian study, it was 7.5 years [8-12].

For Kawasaki’s definition, in addition to persistent fever for a period of five days or more, four out of five mucocutaneous criteria are required, as outlined by the American Heart Association (AHA), published in 2004 (last updated in 2017), which were the same used for studies related to severe acute respiratory syndrome [15]. Despite an undefined etiology, there is suggestive evidence that an infectious agent triggers an inflammatory cascade that leads to Kawasaki disease [16], which
corroborates the current Kawasaki-like findings in the COVID-19 pandemic scenario. Gastrointestinal symptoms, such as lack of appetite, nausea, abdominal pain and diarrhea, were much more frequent in MIS-C than in Kawasaki disease, showing in 100% of cases in the French study [8-11].

Laboratory tests showed neutropenia, lymphopenia, thrombocytopenia and elevated inflammatory markers, both in the group studied in the UK and Italy, with elevated ferritin, hypertriglyceridemia and increased D-dimer, making it more suggestive of MIS-C. The RT-PCR, serology or antigen detection was performed for SARS-CoV-2 detection, and these tests were negative in some patients [8-9].

In the US, and other developed countries, Kawasaki disease is the most common acquired pediatric heart disease in childhood. Of the untreated children, 20% develop coronary aneurysm with a significant increase in the risk of thrombosis and infarction in adulthood. Giant coronary aneurysms can progress to rupture and death. More severe cases can occur with Kawasaki shock syndrome, and rarely with macrophage activation syndrome [7]. In the aforementioned French study, coronary dilation/aneurysm increased from 4 to 13% in patients with classical Kawasaki disease, and to 24% in patients with MIS-C [11].

The treatment of mild cases of MIS-C follows the same pillar of the classic Kawasaki, with immunoglobulin infusion (IVIG) 2 g/kg; in some cases, a repeat dose is administered in resistant cases, or even an adjuvant to corticosteroids, cyclosporine and biological agents, such as anti-interleukin 1, are employed to reduce the development of coronary dilation and other cardiovascular changes [17].

In moderate to severe cases of MIS-C, in addition to IVIG and aspirin, the use of methylprednisolone in the form of pulse therapy is recommended—at a dose of 30 mg/kg/day, for three days, for severe cases, and in moderate cases, 10–20 mg/kg/day for one to three days, followed by a maintenance dose. For refractory cases, following two doses of IVIG and corticosteroids may require biological agents (anti IL-1, anti IL-6 or anti-TNF). The use of anticoagulation is not well established. Mild-to-moderate cases of MIS-C can be managed with a prophylactic dose of enoxaparin and severe cases with a therapeutic dose [18].

Objective
Case report of a pediatric patient who presented pediatric MIS-C, temporarily associated with SARS-CoV-2.

Methods
The information contained in this clinical case description was obtained through clinical record review and interview.

Case Report
Patient JSL, female, five years old, previously healthy, admitted to the Children’s Emergency Room at Hospital Escola de Uberaba-MG, transferred from Araxá, on May 29, 2020, with a history of measured fever for 10 days, with hyperemic macules on the face, hands and foot evolving four days after the onset of the fever. Concomitantly, she presented important conjunctival hyperemia with no secretion and also oral mucosa fissures and a raspberry tongue.
Furthermore, peeling of hands and feet associated with palmoplantar hyperemia was repeated. She had an associated 2 cm cervical swollen lymph node on the right single non-suppurative, not adhering to deep planes—establishment or onset date unavailable. The patient also complained of gastrointestinal symptoms such as nausea, diffused abdominal pain and lack of appetite, besides a headache.

On admission, patient presented with low-grade fever (38.2°C), was hemodynamically stable, oxygen saturation was 98% SpO₂, heart rate (HR) was 121 bpm, GCS was 15, normal cardiac and respiratory auscultation, and diffused but flabby abdominal pain without signs of peritonitis. Due to all the criteria fulfilled for Kawasaki disease, she received 2 g/kg of intravenous immunoglobulin and aspirin at first 50 mg/kg/day, and on the next day, it was increased to 70 mg/kg/day. This was prior to the echocardiography which showed dilatation of the right coronary (Z escore +2.4) and left coronary of preserved diameter, with irregularities in the wall of the anterior descending, and no other abnormalities. From 48 hours after receiving immunoglobulin, she was afebrile, maintaining milder gastrointestinal complaints.

Initially, she presented lateral flow immunochromatography for COVID-19 with IgM negative and IgG positive, Hb 10.6, Ht 33.6%, leukocytes 7.500 (segmented 71.2/eosinophils 22.2/lymphocytes 2.3/monocytes 2.2), platelets 182.000, Na 138, K 3.8, Ca 9.2, P 3.56, urea 16, creatinine 0.5, PCR 60.9, ESR 33, AST 31, ALT 15, CPK 39, and CKMB 29. Furthermore, the chest radiography was normal and blood and urine cultures were negative.

Additional tests were requested after 36 hours of immunoglobulin infusion, according to the following latest recommendations for cases of pediatric MIS-C temporarily associated with SARS-CoV-2, from the Brazilian Society of Pediatrics: Pró-BNP 174, Troponin I 0.003, D-dimer 780, fibrinogen 260, ferritin 295.8, DHL 403, triglycerides 185, HDL 25, and LDL 108; Interleukin screening: IL1b: 7.71, IL2: 2.48, IL4: 8.77, IL 6: 17.03, IL8: 12.62, IL10: 13.86, IL 17: 13.73; TNF-alpha: 6.92; IFN-gama: 6.92.

The serology of a sample collected at admission after immunoglobulin was administered, was only performed on August 24, due to lack of kit, and showed non-reactive IgM and IgG. She remained hospitalized for four days, with remission of complaints and swollen lymph node reduced to 1.5 cm, slight plantar scaling and oral lesions in regression, being discharged for outpatient follow-up and aspirin adjusted to 5 mg/kg/day.

**Discussion**

In view of the current scenario, with new data on the behavior of SARS-CoV-2, the pediatric population has gained prominence for non-respiratory manifestations, despite the lower number of cases in relation to the adult population, and even presenting fatal outcomes. Most cases of pediatric (MIS-C) temporarily associated with SARS-CoV-2 have so far seen non-fatal outcomes; however, with a greater number of cardiac involvement than classical Kawasaki disease, and a greater need for care in the Intensive Care Unit (ICU).

In addition to more frequent gastrointestinal symptoms, it presents laboratory changes mainly of inflammatory markers and higher D-dimer than
Kawasaki disease. Clinical suspicion can be difficult due to the various spectra of the disease, and laboratory tests are not always positive, even at a later time, they can remain negative. Early treatment, given the greater cardiac involvement in MIS-C has become the main pillar in an attempt not to increase the number of acquired heart diseases. Despite the greater number of resistant cases, the majority of MIS-C cases responded well to classic IVIG and aspirin therapy.

The reported patient had all the criteria for Kawasaki disease, gastrointestinal symptoms, coronary artery disease, and a COVID-19 positive IgG antigen test. Despite a late diagnosis, given that the patient was referred after 10 days of fever, she remained hemodynamically stable and responded well to classical therapy. As in most of the cases mentioned in the studies, she did not present any respiratory symptoms reported in the month prior to hospitalization.

**Conclusion**

Further evidence of the increase in the incidence of pediatric MIS-C, temporarily associated with SARS-CoV-2, appears daily, calling pediatricians’ attentions to this new diagnosis with more fatal outcomes than Kawasaki cases (to date). The diagnosis is challenging due to the variety of clinical and laboratory manifestations, with both positive and negative COVID-19 test results, but that should not delay therapy as soon as the diagnostic suspicion is generated. Follow-up is important, as these complications may appear later. We await further studies, given the novelty of the disease to improve the diagnosis and care of the pediatric population.

**References**


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