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CASE REPORT

# Severe Kawasaki disease manifestations in days of COVID-19: case report

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## Abstract

Kawasaki disease is one of the most common primary vasculitis in childhood and main cause of acquired heart disease. It is an acute, multisystemic vasculitis, of unknown etiology, and self-limited, which gained notoriety during the new coronavirus pandemic. High and persistent fever for more than five days, associated with polymorphic rash, bilateral conjunctivitis, tongue erythema with papillary prominence ("strawberry tongue"), extremities edema, and enlarged cervical lymph nodes are typical clinical features of the disease, but these were also found in patients diagnosed with COVID-19 and multisystemic inflammatory syndrome, as well as its main complications: coronary stenosis and aneurysms, myocarditis, heart failure and shock.

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## INTRODUCTION

Kawasaki's disease is one of the most common primary vasculitis in children. It is an acute, multisystemic and self-limited vasculitis, which predominantly affects medium-caliber vessels, with a predilection for coronary arteries, especially in children under the age of 5[1]. It was initially described by Tomisaku Kawasaki in 1967 as a benign and self-limited disorder, with severe coronary changes, heart failure and death later, if not properly treated[2].

Although 85% of cases are reported in children under 5 years of age, it can affect all age groups, with a greater risk of cardiovascular sequelae from the age of eight. It is more frequent in boys, being the main cause of heart disease acquired in children in the United States, where the estimated incidence is 25 cases for every 100,000 children under five years old. In Asian countries, this incidence is even higher, reaching 30.3 per 100,000[2-3].

Although its etiology is not well defined, some hypotheses try to explain its development. Some authors believe that it is triggered by agents that cause asymptomatic or oligosymptomatic infections in children, especially RNA-type viruses, resulting in disease in genetically susceptible individuals, although early studies have provided evidence of immune stimulation by bacterial superantigens, as well as an IgA oligoclonal response; however, much has been said about the NL-63 coronavirus theory, which gained strength after reports of the disease in patients affected by COVID-19[4-6].

In December 2019, the World Health Organization was notified due to an outbreak of pneumonia of unknown origin in the city of Wuhan, China. Later, the etiologic agent was identified; it was a new type of coronavirus, which was called SARS-CoV 2[7]. In the midst of a pandemic, the case of a 6-month-old child diagnosed with Kawasaki disease was published, who was also positive for COVID-19. Thereafter, numerous reports of a severe syndrome, with initial manifestations similar to Kawasaki's disease, which appeared about fourteen days after the infection with the new coronavirus were published, receiving the name of pediatric multisystemic inflammatory syndrome temporarily associated with SARS-CoV-2 (MIS-C)[8].

The case reported below illustrates Kawasaki's disease in its classic form, and its severe manifestations. Given the negative serology results (IgM and IgG) and RT-PCR (Polymerase Chain Reaction with Reverse Transcription) for COVID-19, it does not fit the criteria for defining the MIS-C, but its main diagnosis must be considered in the differential. Our goal is to alert the reader to the peculiar characteristics of Kawasaki's disease, which can confuse many professionals in times of pandemic, its potential for severity and the need for early and specific diagnosis, directing treatment in order to avoid its complications.

The patient's guardian authorized the use of data from the medical record and photos in this report, upon signing the Free and Informed Consent Form; it was submitted to the Research Ethics Committee through the Brazil Platform.

## CASE PRESENTATION

The patient was a male, 3 year-old, preschooler, previously healthy, having continuous fever for 5 days, developing a non-pruritic polymorphic rash (Figures 1 and 2) on the fourth day, rash-type on the chest and back, and maculopapular erythema on the upper and lower limbs . He was admitted to the pediatric ward using antihistamines and steroids to treat the skin lesions.

Upon admission, he was in regular general condition, dehydrated, pale (+/4+), feverish and eupneic. His Glasgow coma scale was equal to 15, isochoric and photoreagent pupils, and bilateral bulbar conjunctival hyperemia, without secretion. His mouth was red and he had fissures in the lips, enanthema, hypertrophy and hyperemia of the tonsils, in addition to hyperemia of the tongue with prominent papillae. He had a palpable submandibular lymph node on the left, without signs of inflammation.

After twelve hours in the outpatient ward, the rash became more intense and the hands were swollen. He was moaning, saturating 88% in room air and 92% in the Venturi mask at 50%, systolic blood pressure of 80 mmHg, diastolic 45 mmHg and average 60 mmHg, evolving with tachypnea and respiratory effort. He was referred to the pediatric intensive care unit (PICU) in respiratory failure, being promptly intubated, and connected to mechanical ventilation, with a central access in the right internal jugular vein, started on Cefepime empirically, 150 mg/kg /day divided into three doses, samples submitted to laboratory tests and cultures (Chart 1).



**Figure 1.** Edema and fissure of the lips and polymorphic rash on the chest and abdomen.



**Figure 2.** Polymorphic rash in the lower limbs.

**Table 1**. Laboratory tests collected upon admission to the Pediatric Intensive Care Unit (PICU).

| |
|---|
| CBC |
| • Hemoglobin: 7,3g/dl |
| • Hematocrit: 21% |
| • White cells: 20.000/mm³ |
| (Rods: 18%; Segmented: 69%) |
| • Platelets: 362.000/mm³ |
| Sodium: 138mmol/L |
| Potassium: 3,3mmol/L |
| Calcium: 9,0mmol/L |
| Magnesium: 1,9mmol/L |
| Glucose: 108mg/dL |
| Bilirubins: 1,0mg/dL (indireta: 0.4 mg/dL) |
| TGO: 30U/L |
| TGP: 25U/L |
| Ferritin: 645µg/L |
| ESR: 56mm |
| PCR: 499mg/L |
| Triglycerides: 205mg/dL |
| Ureia: 0.4 mg/dL |
| Creatinina: 0.4 mg/dL |
| TTPA: 30 |
| TP: 1.82 |
| Fibrinogen: 447g/L |
| Troponin: 29.4 ng/mL |
| CSF |
| • Red blood cell: 1 |
| • Leucocytes: 28 (60% neutrophils; 35% monocytes) |
| Cultures |
| • Blood cultures 2 samples (central and peripheral): Negative |
| • Uroculture: Negative |
| • CSF culture: Negative |
| COVID-19 |
| • IgM: Negative IgG: Negative RT-PCR: Negative |

He remained stable on the first day of admission to the unit; however, on the second day he required an increase in ventilatory parameters, with bradycardia, hypotension (systolic: 66 mmHg; diastolic 35 mmHg; average: 45 mmHg), cold limbs, capillary filling time of 5 seconds and reduced diuresis. He received two volume expansions of 20 ml/kg associated with epinephrine 0.3 mcg/kg/minute in continuous infusion. We ran a bedside echocardiogram, which showed a slight dilation of the heart chambers, with a reduction in left ventricular segmental contractility, with an ejection fraction of 43%, without coronary changes.

In view of the clinical history and physical examination data, there were two initially suggested diagnostic hypotheses: toxic shock syndrome and multisystemic inflammatory syndrome, possibly related to the coronavirus. We then started him on Clindamycin 40 mg/kg/day every 6/6 hours and ordered an RT -PCR and serology for COVD-19 (IgM and IgG). After the laboratory test results, we administered red blood cell concentrate 10 ml/kg; vitamin K 1mg/kg and furosemide 1 mg/kg, with good diuresis thereafter.

On the third day of intensive care (8th day of symptoms), he remained feverish, despite the antibiotic therapy, with negative blood culture, urine culture and CSF culture. RT-PCR, IgM and IgG for COVID-19 were negative. There were CSF changes without growth of microorganisms in the culture, suggesting aseptic meningitis. Then we opted to infuse Immunoglobulin 2g/kg in twelve hours, associated with the administration of Acetylsalicylic Acid 100 mg/kg/day, considering the possibility of myocarditis secondary to Kawasaki's disease as the cardiogenic shock etiology.

After five days in the PICU (10th day of symptoms), he had fever remission (48 hours of immunoglobulin), making it possible to decrease the ventilatory parameters and titrate the vasoactive drug until its suspension. We reduced the dose of ASA to 5 mg/kg/day and proceeded to extubation. He was taken to the outpatient ward on the eighth day of hospitalization, where he remained for another four days, and on the 16th day of the illness his fingers and toes began to peel off.

## DISCUSSION

The most accepted etiopathogenic hypothesis to date is that infectious agents that determine clinical manifestations in susceptible individuals trigger Kawasaki's disease. There were inflammatory changes in several organs, mainly

in the heart, pericardium and blood vessels, causing myocarditis, pericarditis, aneurysms and coronary strictures. Aseptic meningitis, pneumonitis, lymphadenitis and hepatitis are not uncommon[2,4,10].

The reported case portrays the characteristics and diagnostic criteria of Kawasaki disease (Chart 2), which is divided into three clinical phases: acute, subacute and convalescence. High, persistent fever happens on the first day of the disease. These children are often examined in emergency units, where antibiotics are prescribed empirically, which does not stop the fever and leads to the patient's return[2].

The presence of fever for 5 days or more, associated with at least 4 of the other 5 criteria characterizes the classic form, also called complete Kawasaki's disease. However, febrile patients who do not have all of these clinical features are often considered to have the incomplete (or atypical) form of the disease, and should undergo echocardiography[2].

In the face of numerous warning notes from medical societies and scientific publications on pediatric multisystem inflammatory syndromes temporarily associated with SARS-CoV-2, the differential diagnosis with severe forms of Kawasaki disease must be promptly established, since the signs and symptoms are similar, and have similar outcomes. In addition to MIS-C, one must consider other differential diagnoses. Here we stress the toxic shock syndrome, whether staphylococcal or streptococcal, with similar clinical characteristics, but differences in treatment, may delay the initiation of immunoglobulin therapy, resulting in the maintenance of hypoperfusion status, and increased morbidity and mortality[8-9].

Bilateral and non-secretive bulbar conjunctivitis, associated with fever and rash, often confuse the examiner, given similarity with other viral rashes, bacterial infections and pharmacodermia. The rash appears until the fifth day of the disease, it is nonspecific and polymorphic; it ranges from maculopapular erythema to urticaria, purpuric or scarlet fever rash. Enanthema and cleft lip are frequent. Erythema and papillary hypertrophy make the tongue "strawberry-like". Unilateral cervical lymphadenopathy in the anterior cervical triangle is also common in the disease[3].

**Table 2.** Diagnostic criteria for Kawasaki's Disease[2]

| **Fever for 5 days, with at least 4 of the following 5 criteria:** |
|---|
| 1. Non-purulent bilateral bulbar conjunctivitis; |
| 2. Strawberry-like tongue, erythema, enanthema or labial fissure; |
| 3. Eritema e edema de mãos e pés na fase aguda ou descamação periungueal na fase subaguda; |
| 4. Exantema escarlatiniforme, morbiliforme ou polimórfico; |
| 5. Linfonodomegalia cervical ≥1,5cm, geralmente unilateral. |

**Source:** adaptado McCrindle et al.[2].

Laboratory tests can show characteristic findings (Chart 3), just as the electrocardiogram can show arrhythmias, PR interval prolongation and nonspecific changes in the ST segment and the T wave[2-3].

The subacute phase is marked by desquamation of the nail, extremities and perineal region. The risk of sudden death increases with the remodeling and thrombocytosis of the middle layers of the coronary arteries, favoring the formation of calcifications, stenoses and thrombi. Convalescence, on the other hand, begins with the improvement of clinical signs, and lasts from six to eight weeks, until the normalization of inflammatory tests; however, the temporal evolution of the disease can be shortened with specific treatment[10].

Almost 70% of the patients have myocarditis. Its severity can result in abnormal contractility, heart failure and shock if adequate treatment is not established in the first days of the acute phase. The change in the level of consciousness, tachycardia, tachypnea and changes in peripheral perfusion can represent early signs of myocardial dysfunction, evolving rapidly with cold extremities, thin pulses, diaphoresis, and cyanosis, canter rhythm, crackling rales, hepatomegaly, jugular stasis and peripheral edema[9-10].

Treatment in the acute phase aims to reduce the inflammatory response and prevent vasculitis and its consequences, while in the subacute and convalescence phase it aims to prevent ischemia and infarction. The treatment of choice is immunoglobulin, at a dose of 2 g/kg associated with acetylsalcylic acid (ASA) 100 mg/kg, and should be used preferably in the first ten days of the disease, and ASA maintained until convalescence in those patients without coronary aneurysm[3,11].

Cardiac function and fever improve within 72 hours after the immunoglobulin infusion. Approximately 10% of patients do not respond to initial therapy, and in these cases,

**Table 3.** Common laboratorial findings in Kawasaki's disease.[2]

| |
|---|
| •Leukocytosis with neutrophilia and left shift; |
| •Normocytic and normochromic anemia; |
| •Increase in ESR (erythrocyte sedimentation rate); |
| •Increased CRP (C-reactive protein); |
| •Thrombocytosis; |
| •Moderate increase in transaminases; |
| •Hypoalbuminemia; |
| •Sterile pyuria; |
| •CSF with pleocytosis with a predominance of mononuclear; |
| •Hyponatremia; |
| •Synovial fluid with leukocytosis. |

**Source:** adapted from McCrindle BW et al. Circulation. 2017;135:e927–e999.[2].

pulse therapy with corticosteroids or immunosuppressants, such as cyclophosphamide and cyclosporine is indicated[12]. Studies still in progress show promising results with the use of Infliximab and Etanercept[13-14]. Plasmapheresis is effective in reducing the incidence of aneurysms, but given the risks related to the procedure, it should not be performed routinely[15].

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