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CASE REPORT

KAWASAKI DISEASE WITH ATYPICAL INITIAL SYMPTOMS: A CASE REPORT

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Abstract

Introduction: Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of unknown etiology. The diagnosis is essentially clinical and the treatment is based on the use of intravenous human immunoglobulin (IVIG) and acetylsalicylic acid (ASA) in anti-inflammatory dose, being ideally initiated by the tenth day of the onset of symptoms in order to avoid the complications associated with this pathology. **Metodology:** This is a case report of a 9-year-old child with Kawasaki syndrome with atypical initial presentation. **Discussion:** Previously healthy child, presenting febrile jaundice hemorrhagic syndrome and influenza syndrome, associated with radiological changes that could be correlated with SARS-COV-2 infection, without initially ruling out the hypothesis of Pediatric Multisystemic Inflammatory Syndrome (SIM-P). After negative serologies and cultures, there was a progressive remission of symptoms, except for the fever. Criteria for KD were met on the 16th day of evolution, when monotherapy with ASA without IVIG was initiated, with resolution of the fever. **Conclusion:** It is essential to be aware of the possible variations in the clinical presentation of KD and correlate it with the epidemiological and social context of the patient, due to the morbidity related to this vasculitis.

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INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of unknown etiology. There is a slight predominance in males and in children under five years of age, with 80% occurring in children under four years of age; and the peak incidence occurring between nine and eleven months.[1]

The diagnosis is essentially clinical and there are no specific laboratory tests for the disease. Less commonly, some patients may progress to an atypical or incomplete form, not meeting all the proposed requirements or leading to delayed diagnosis and treatment.[1,2]

Pediatric Multisystem Inflammatory Syndrome (PMIS) emerged with the COVID-19 pandemic. In patients with KD criteria and current or recent diagnosis of COVID-19, the hypothesis of PMIS should be considered as they share several clinical and laboratory characteristics, but with specific therapeutic guidance and complications.[3]

Due to the importance of this pathology, below is a case report of a patient with KD with an atypical clinical presentation with epidemiological factors strongly suggestive of infectious diseases.

CASE REPORT

G.V.F.S, 09 years old, male, mixed race, born and living in Serra/ES, usual weight of 24,800 kilograms (kg), height 136 centimeters (cm). Previously healthy, vaccination schedule up to date, no history of allergies, previous surgeries or hospitalizations and no family history of rheumatological, oncological, autoimmune or autoinflammatory diseases. Resident in AN urban area, brick house, does not have filtered water and the sanitary conditions near his house are precarious (open sewage, with rats and many insects).

His clinical condition began with neck pain on the right, hyporexia, and diffuse abdominal pain that progressed to fever associated with a non-pruritic maculopapular rash. On the third day of symptoms, he received medical attention at the Emergency Care Unit (UPA) in his municipality, with leukocytosis with left shift, elevated CRP (100 mg/dL) and increased liver transaminases (TGO 230 IU/L and TGP 170). IU/L, treatment with Amoxicillin-Clavulanate was initiated and a reassessment was requested in 48 hours. There was improvement in the rash, persistence of fever that only ceased with the use of antipyretic, increased intensity of abdominal pain in the right hypochondrium and epigastrium associated with jaundice, macroscopic choluria/hematuria and headache.

During reevaluation, high levels of transaminases were maintained and investigation was complemented with canalicular enzymes and measurement of total bilirubin and fractions showing a cholestatic pattern: TGO 63.5 IU/L; TGP 114.5 IU/L; GGT 693.1UI/L; FA 522 IU/L; BT 4.71 mg/dL; BD 3.89 mg/dL; BI 0.82 mg/dL. Referred for hospitalization at the state's reference children's service for work-up and clinical support. Upon finding himself jaundiced and dehydrated, he initially considered the possibility of leptospirosis due to the strongly positive epidemiological link. He was then started on Ceftriaxone and clinical support measures. Investigation carried out for other possible differential diagnoses, such as serology for viral hepatitis, arboviruses and infectious diseases.

On the seventh day, flu-like symptoms such as cough and runny nose began. He was in regular general condition, hydrated, pale, prostrated, with inappetence, jaundiced (++/4+), with persistent fever and hematuria, periorbital edema and right hand edema. No cardiovascular changes. He also had reduced vesicular sounds in the lung bases, tachypnea and absence of respiratory distress. He was ascitic and had a painful abdomen in the epigastrium and right hypochondrium, hepatomegaly 3 cm from the right costal margin. He developed oliguric acute renal failure responsive to volume expansion and furosemide and, due to clinical worsening, we decided to escalate his antibiotic therapy to Cefepime. Abdominal ultrasound was performed and mild hepatomegaly was confirmed, ascites, asymmetric thickening of the bladder wall, presence of debris inside the bladder with pus or blood. The chest X-ray showed diffuse interstitial infiltrate, complemented by computed tomography which showed small peribronchial consolidations, bilateral pleural effusion, ground glass areas and reactive mediastinal lymph nodes. Due to the current epidemiological context, RT-PCR for COVID-19 was collected and transferred to the flu syndrome cohort sector of the service.

He kept his regular general condition with persistence of daily fever. Doxycycline was associated to cover for rickettsiosis, as the patient had a history of recent ingestion of fresh milk. Laboratory tests showed improvement in liver transaminases and renal function, but maintained leukocytosis, thrombocytosis, elevated inflammatory markers, hypoalbuminemia, sterile pyuria, negative cultures and non-detectable COVID 19 RT-PCR. Transthoracic echocardiography (TTEC) was performed on the 12th day of symptom evolution, and it came back normal.

On the 14th day, he was transferred to this service (Cassiano Antonio de Moraes University Hospital– HUCAM) and upon admission he was in regular general condition, prostrated, feverish, with non-exudative conjunctivitis, cleft lip, hypertrophy of taste buds , edema and peeling of hands and feet. In control exams he presented an altered coagulogram: TAP 50%; PTT 59 seconds, the decision was made to start vitamin K. The fever lasted until the 16th day of symptoms, when the diagnostic hypotheses were expanded to KD or PMIS, despite a negative test for SARS-COV2 we could not rule out PMIS, as patients who meet full or partial criteria for Kawasaki can be included in the PMIS hypothesis.

On the 18th day after the opinion of the Pediatric Rheumatologist, the presence of diagnostic criteria for KD was retroactively confirmed: fever lasting five days or more, cervical lymph node enlargement, oral changes (hypertrophied papillae), changes in the limbs (edema and desquamation), skin

rash, non-exudative conjunctivitis, leukosis, thrombocytosis, increased transaminases, hypoalbuminemia, ultrasound changes in the gallbladder and sterile pyuria. Due to late diagnosis and unchanged ECOTT, in addition to the patient being afebrile for more than 48 hours, there was no indication for administration of IVIG. Acetylsalicylic acid (AAS) was started in an antiplatelet dose with IVIG planned in case of new febrile episodes.

Antibiotic therapy was suspended after negative cultures and serology. He was discharged from hospital after twenty-six days of hospitalization, using Aspirin at an antiplatelet dose, with outpatient referral to the service's pediatric rheumatology department. During follow-up with the specialty, the TTEC was repeated, where right coronary artery dilation and sustained thrombocytosis were detected. Therefore, he remained on AAS as monotherapy.

DISCUSSION

KD is an inflammatory syndrome with variable clinical presentation. It is the leading cause of pediatric acquired heart disease in developed countries and the second most common vasculitis in childhood, after Henoch-Schonlein purpura. The etiology is complex and poorly understood.[1,2] Its pathophysiological pathways may be associated with a response to a classical antigen, with activation of both innate and adaptive immunity and serum elevation of pro-inflammatory agents. It has been established that there is a genetic and racial (Asian) predisposition, with increased risk in first-degree relatives of affected individuals and twins. More consistently, there are reports of a correlation in the etiology of KD with infectious diseases, suggesting microorganisms such as Streptococcus, Staphylococcus, Mycoplasma and various viral agents, including strains of coronavirus.[2,3,4]

The diagnosis is based on clinical criteria established by the American Heart Association (AHA) and are described in table 1.[4]

Around 20% to 30% of patients do not meet the classic Kawasaki diagnostic criteria, but have suggestive laboratory changes, corresponding to an incomplete or atypical clinical form of the disease. They are: ESR >40mm/1st hour, CRP > 3mg/dL; platelets > 450,000/mm3 (after 7 days of illness); anemia; leukocytosis > 15,000/mm^3; TGP > 50U/L; albumin < 3g/dL; sterile pyuria; hyponatremia; and coronary dimensions through Z-score > 2.5 on echocardiogram.[1,5] Therefore, it is important that the anamnesis is detailed and the physical examination thorough, and signs and symptoms may be found sequentially or at different times.

Incomplete KD has a higher incidence in infants under six months of age, possibly due to immunological immaturity in the face of vasculitis, combined with a neutralizing action of maternal antibodies against antigens and a cross-reaction of the active immunity itself.[5] KD with atypical symptoms is difficult to diagnose and presents a higher risk of coronary anomalies and other complications such as decreased coronary artery compliance, pericarditis, myocarditis, arrhythmias, ischemic heart disease, pericardial effusion, valve regurgitation and sudden death. There may be myocardial injuries regardless of coronary arteries involvement.[5,6]

According to the World Health Organization (WHO), the criteria proposed for the diagnosis of PMIS are described in table 2.

Other causes of bacterial infections must be ruled out, in addition to confirming the diagnosis of COVID 19, whether by RT-PCR, antigen test or positive serology, or contacts of people infected by SARS-COV-2[7].

PMIS should be a hypothesis when there is persistence of the febrile condition, laboratory markers of inflammatory activity (increased CRP, ESR, d-dimer, ferritin, DHL, IL-6, procalcitonin) and evidence of dysfunction of one or more organs, as well as such as reduced fibrinogen, hypoalbuminemia, lymphopenia and neutropenia. Despite the clinical and laboratory similarities, there are also substantial differences in the age range of involvement: children aged 10 years in PMIS and 2 years in KD. Clinically in PMIS there is a lower prevalence of classic signs of KD and its manifestations are more severe, due to the intensity of inflammation, characterized by shock. Another characteristic is the more frequent gastrointestinal symptoms, myocardial and renal dysfunction in PMIS.[7,8,9]

Given the severity and importance of the approach, and the initiation of early treatment, it is essential that pediatricians consider Kawasaki disease as a differential diagnosis of PMIS. The difficulty lies in defining whether or not the patient presents diagnostic criteria for PMIS.

All patients meeting AHA criteria should be treated. This also applies to children with suspected incomplete KD, given the low risks associated with the administration of IVIG and the high risks of developing coronary artery aneurysms.[10-12] Corroborating this case report, an update highlighting the similarities and differences between PMIS and complete or incomplete KD, as well as the approach to these cases. For better analysis and understanding, we created an approach flowchart (figure 1).[13]

In this case report, the patient was cholestatic and had persistent fever for more than five days, but the appearance of other clinical criteria occurred gradually and asynchronously, associated with a strong epidemiological context of infectious diseases. Still in this case, during the course of the disease there were criteria for flu-like syndrome and in the current pandemic context, infection by SARS-COV-2 and PMIS are important differential diagnoses.

KD treatment aims to reduce inflammation and arterial damage, preventing thrombi in patients with already established coronary lesions[4]. It is based on the use of IVIG, preferably introduced by the tenth day of fever, associated with the use of acetylsalicylic acid (ASA) in an anti-inflammatory dose. After 48 hours of feeling afebrile, it is

Chart 1. Diagnosis of Classic Kawasaki Disease

Classical KD is characterized by having fever for at least 5 days (the day of fever onset is considered as the first day of fever) along with at least 4 of the following 5 main clinical features. In the presence of ≥ 4 main clinical features, especially when edema of the hands and feet is present, the diagnosis of KD can be made with 4 days of fever, although medical specialists who have treated many patients with KD can establish the diagnosis with 3 days of fever in rare cases:
1. Erythema and fissure of the lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa;
2. Bilateral conjunctivitis without exudate
3. Rash: maculopapular erythroderma, diffuse erythroderma, or erythema multiforme
4. Erythema and edema of the hands and feet in the acute phase and/or periungual peeling in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral
A careful history may reveal that ≥1 major clinical features were present during the illness but resolved at the time of presentation.
Patients who lack complete clinical features of classic KD are often evaluated for incomplete KD. If abnormalities in the coronary arteries are detected, the diagnosis of KD is considered confirmed in most cases.
Laboratory tests typically reveal a normal or elevated white blood cell count with a predominance of neutrophils and an increase in acute phase tests such as C-reactive protein and erythrocyte sedimentation rate during the acute phase. Hyponatremia, hypoalbuminemia, elevated liver transaminases, and sterile pyuria may be present. In the second week after the onset of fever, thrombocytosis is common.
Other clinical findings may include the following:
• Cardiovascular: Myocarditis, pericarditis, valve regurgitation, shock, abnormalities of the coronary arteries, aneurysms of medium-sized non-coronary arteries, peripheral gangrene, enlargement of the aortic root;
• Respiratory: Peribronchial and interstitial infiltrates on chest x-ray and pulmonary nodules;
• Musculoskeletal: Arthritis, arthralgia (synovial fluid pleocytosis);
• Gastrointestinal: Diarrhea, vomiting, abdominal pain; Hepatitis, jaundice; Gallbladder dropsy and pancreatitis;
• Nervous system: Extreme irritability; Aseptic meningitis (cerebrospinal fluid pleocytosis); Paralysis of facial nerves; Sensorineural hearing loss;
• Genitourinary: Urethritis/cystitis, hydrocele;
• Others: Destructive eruption of the groin; retropharyngeal phlegmon; anterior uveitis by slit lamp examination; erythema and induration at the BCG inoculation site;
The differential diagnosis includes other infectious and non-infectious conditions, including the following:
Measles;
Other viral infections, for example: adenovirus and enterovirus;
Toxin-mediated staphylococcal and streptococcal diseases (e.g., scarlet fever and toxic shock syndrome);
Drug hypersensitivity reactions, including Stevens Johnson Syndrome;
Systemic onset juvenile idiopathic arthritis;
With epidemiological risk factors: Rocky Mountain spotted fever or other infections such as Rickettsia and Leptospirosis.

Source: Adapted from McCrindle et al. 2017[4].

recommended to adjust the ASA to the antiplatelet dose, and should be maintained for up to eight weeks, or longer in case of coronary abnormalities, until there is stability and absence of luminal expansion of the coronary arteries.[4,6]

The AHA suggests that in patients at high risk of coronary aneurysms, adjuvant treatment with intravenous methylprednisolone 2mg/kg/day should be considered until fever resolves and subsequent continuation with oral prednisolone. Corticosteroid withdrawal can be carried out over two to three weeks.[1]

Despite having a generally benign course, KD can have d to serious complications, the most significant being coronary artery injury, in addition to pericardial effusion, mitral failure, congestive heart failure, myocardial systolic dysfunction and systemic vasculitis. Complications are responsible for increased mortality and morbidity in children if not identified and treated early.[10] Around 15% to 25% of untreated patients and 5% of treated patients develop lesions in the coronary arteries. A small proportion of patients do not respond to therapy and may become refractory.[2,6] Early treatment with IVIG has been shown to reduce the incidence of coronary aneurysm and complications associated with untreated KD can be fatal.

Due to the clinical and laboratory similarities involving KD (complete and incomplete) and PMIS, being able to identify the entire possible clinical spectrum and treat in a targeted and safe manner results in a reduction in hospitalization and favors a better prognosis.

In this case, we highlight the initial atypical development associated with the strongly positive epidemiological link, which led to a delay in diagnosis and specific treatment within the ideally recommended time, reducing the possibilities of preventing complications associated with this disease.

Chart 2. Case definition for Pediatric Multisystem Inflammatory Syndrome (PMIS)

Case that was hospitalized or died with:	
Presence of high fever (consider a minimum of 38.0° C) and persistent (≥ 3 days) in children and adolescents aged 0 to 19 years.	
AND	• At least two of the following signs and symptoms: • Non-purulent conjunctivitis or bilateral rash or signs of mucocutaneous inflammation (oral, hands and feet); • Arterial hypotension or shock; • Manifestation of myocardial dysfunction, valvulitis or coronary abnormalities (including echocardiogram findings or elevated Troponin/NT--proBNP); • Evidence of Coagulopathy (due to elevated PT, aPTT, D-dimer); • Acute gastrointestinal manifestations (diarrhea, vomiting or abdominal pain).
AND	elevated inflammatory markers, ESR, CRP or procalcitonin, among others.
AND	any other causes of obvious infectious origin of inflammation have been ruled out, including bacterial sepsis, staphylococcal, or streptococcal shock syndrome.
AND	Evidence of COVID-19 (molecular biology, positive antigen or serological test) or history of contact with a COVID-19 case.
Additional Comments: Children and adolescents who meet full or partial criteria for Kawasaki syndrome or toxic shock, with a history of COVID-19, may be included	

Source: Adapted by the Ministry of Health, based on the PAHO/WHO case definition, validated by the Brazilian Society of Pediatrics, Brazilian Society of Cardiology and Evandro Chagas Institute[7].

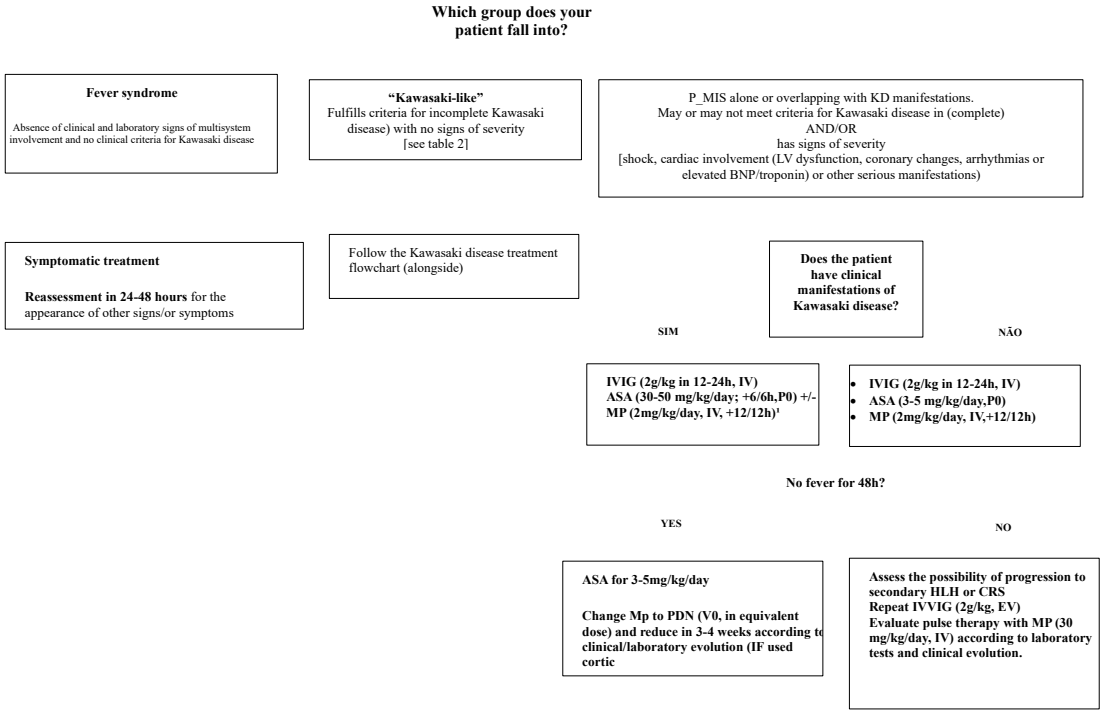


Figure 1. PMIS[13] treatment flowchart.
Legend: IVIG: Intravenous human immunoglobulin; ASA: Acetylsalicylic acid; MP: Methylprednisolone; PDN: Prednisone; PO: Oral administration; IV: Intravenous route; HLH: hemophagocytic lymphohistiocytosis; CRS: Cytokine release syndrome (cytokine storm syndrome[1]; **If the patient have risk factors for immunoglobulin resistance. For Asian patients or in locations with validation of the Kobayashi criteria (score ≥5)**: sodium ≤133mmol/L (2 points); aspartate aminotransferase ≥100UI/L (2 points); C-reactive protein ≥10mg/dl (1 point); neutrophils ≥80% (2 points); platelets ≤300,000/mm^3 (1 point); days of illness ≤4 (2 points); age ≤12 months (1 point). **Non-Asian patients considered at high risk of IVIG resistance** if they have 1 or more of the following criteria: enlarged coronary arteries (Z score >2.5-3) at presentation (prior to treatment with IVIG); age ≤12 months; shock; multiple activation syndrome.
Source: Campos L, Almeida R, Goldenzon A, Rodrigues M, Sztajnbok F, Lino K, Nogueira K, Silva R, Fonseca A.13

CONCLUSION

We emphasize with this report that we cannot fail to include atypical KD as a differential diagnosis, since vasculitis in children can present with signs and symptoms common to other possible pathologies, hampering diagnosis and, therefore, the institution of a proper therapy. The morbidity of this vasculitis becomes significant if it is not identified and intervened early on.

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