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Pediatric inflammatory multisystem syndrome or Kawasaki disease - continuous challenges in Pediatrics - case report

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ABSTRACT

Introduction. Kawasaki disease (KD) and pediatric inflammatory multisystem syndrome (PIMS) are similar vasculitis conditions affecting medium and small vessels, particularly the coronary arteries. This study aimed to highlight diagnostic and treatment challenges in a case initially diagnosed as PIMS, which evolved into atypical KD.

Materials and methods. A 2-year-10-month-old male was admitted with a high fever persisting for 6 days, unresponsive to antipyretics.

Results. On admission, the patient exhibited a poor general condition, pale skin, non-pruritic erythematous rash, and enlarged, non-painful lymph nodes. Laboratory tests showed elevated inflammatory markers, leukocytosis with neutrophilia, hypoalbuminemia, liver enzyme abnormalities, altered cardiac markers, and elevated D-dimers, but no initial echocardiographic changes. Positive SARS-CoV-2 antibodies led to an initial PIMS diagnosis, and treatment with intravenous methylprednisolone, antiplatelet, anticoagulant therapy, and hepatoprotective agents was started. The patient's condition initially improved but then worsened with febrile spikes, rash, neutropenia, thrombocytopenia, anemia, and coronary artery dilation on echocardiography. This led to a diagnosis of KD with atypical onset, and treatment with immunoglobulin, antiplatelet, and anticoagulant therapy was initiated. The patient's condition improved slowly.

Conclusions. KD and PIMS share overlapping characteristics, making them difficult to distinguish. There is no definitive criterion to differentiate KD and PIMS, leading to potential diagnostic errors.

Keywords: child, Kawasaki disease, PIMS, COVID-19, hyperinflammation, treatment

INTRODUCTION

Kawasaki Disease (KD) is an acute inflammatory illness that targets medium and small arteries, particularly those in the coronary system [1]. It is among the most common types of vasculitis in children and adolescents. The disease has the highest incidence rate in Asia, particularly in children under 5 years of age, and the lowest incidence rate in Europe [2]. KD predominantly occurs in young children, with most cases occurring between the ages of 6 months and 5 years, though it is not exclusive to this age group [3]. The coronary arteries are the most commonly affected by KD, which can result in aneurysms and long-term cardiovascular complications. Consequently, KD is one of the primary causes of acquired heart disease in children in developed countries [4]. The etiology of KD has remained unknown for decades; earlier theories proposed that an unidentified infectious pathogen triggers the disease and are still somewhat accepted. However, it is now more likely that known viral agents and genetic predisposition, coupled with an abnormal immune response, play a significant role in the devel-

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opment of KD [5]. KD is diagnosed based on clinical criteria and by ruling out other possible causes, as there are no specific markers for the disease. Typically, the classic form of KD features a fever lasting at least 5 days, along with 4 or more of the following clinical signs: a polymorphous rash, changes in the oral mucosa (cracked lips or strawberry tongue), cervical lymphadenopathy, bilateral non-exudative conjunctivitis, and changes in the extremities such as palmar and plantar erythema, desquamation, or edema. Incomplete KD is characterized by fever with insufficient clinical criteria, but may still lead to coronary artery aneurysms, while atypical KD is defined by fever accompanied by clinical manifestations different from the typical form [6]. Beyond the classic criteria, KD can present with additional features such as arthritis, uveitis, pancreatitis, abdominal pain, jaundice, or neurological symptoms, which can contribute to delays in diagnosis.

Treatment of KD involves the administration of intravenous Immunoglobulin (IVIG) at a dose of 2g/kg/body weight/24 hours. Early treatment with IVIG has shown to reduce cardiac complications in 4-6% of patients when combined with aspirin at a dose of 30-50 mg/kg/body weight/day during the febrile episode, followed by a reduction of the dose to 3-5 mg/kg/body weight/day, especially if coronary aneurysms occur. Additionally, in such cases, antiplatelet and anticoagulant therapy are also recommended. However, there are KD cases, approximately 10-20%, that do not respond to the initial dose of IVIG, in which case a second dose is recommended, along with methylprednisolone pulsed therapy at 30 mg/kg/day, maximum 1 g/day, for 3 days. Other therapeutic options include Infliximab, cyclosporine, or Anakinra, although there is no clear data regarding the optimal choice [7-9].

Pediatric Inflammatory Multisystem Syndrome (PIMS) in children and adolescents emerged during the SARS-CoV-2 pandemics, with the UK National Health Service being the first to recognize this aspect on April 25th, 2020 [10]. Since then, numerous studies and research have been conducted in regions with a high incidence of severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2), where multiple cases of PIMS have been documented. These patients often fulfill the criteria for KD as defined by the American Heart Association [11-14]. Thus, clinical manifestations include persistent fever, mucocutaneous involvement, lymphadenopathy, gastrointestinal symptoms, and often cardiovascular dysfunction [15].

The first-choice therapy for PIMS comprises a combination of intravenous immunoglobulin and intravenous methylprednisolone at a dose of 1-2 mg/kg/body weight/day, plus low-dose aspirin at 3-5 mg/kg/body weight/day in all patients without hemorrhagic risk. Unlike KD, a second dose of intravenous immunoglobulin is not indicated. If refractory disease is suspected, treatment with methylprednisolone pulsed therapy or consideration of Infliximab or Anakinra therapy is recommended [16].

Considering all these aspects, we have chosen to present a case that highlights the differences between KD and PIMS. The aim of this case report was to highlight the difficulties encountered when dealing with a case of PIMS that also exhibits characteristics of KD.

CASE REPORT

Reasons for Admission

We present the case of a 2 years and 10-month-old male, who was admitted to the Pediatric Clinic I, Targu Mures due to high fever persisting for 6 days, which responded poorly to antipyretics, along with rhinorrhea and dysphagia. The patient had received symptomatic treatment and antibiotics being admitted at the territorial hospital, but without improvement. Although, the rapid antigen test for SARS-CoV-2 was negative, from the medical history, we noted that the patient's mother had experienced respiratory symptoms with anosmia and ageusia approximately 3 weeks prior to the child's admission.

Physical Examination

The physical examination at the time of admission revealed a compromised general status, the patient being afebrile at admission, presenting with a distressed appearance, with a crying and tired face, pale skin, erythematous rash without pruritus, non-confluent on the anterior part of the thorax, bilateral laterocervical and submandibular adenopathies, non-painful to palpation, with balanced cardiac and respiratory functions, without signs of meningeal irritation, weighing 12 kg upon admission.

Evaluation and Diagnosis

Clinical examination at 24 hours post-admission revealed a compromised general status, facial asymmetry, prompting a neurological consultation which interpreted the symptoms as peripheral right-sided facial palsy post-COVID, recommending symptomatic treatment. Laboratory tests performed at admission showed elevated inflammatory markers (C-reactive protein: 138 mg/l, erythrocyte sedimentation rate: 95 mm/h), leukocytosis (19.040x10^3/µl) with neutrophilia (16.090x10^3/µl, 84.5%), hypoalbuminemia (3.47 g/dl), hepatic cytolysis syndrome (aspartate aminotransferase 775 U/L, alanine aminotransferase 459 U/L, gamma glutamyl transferase 645 U/L), positive cardiac markers (Troponin I 41,6 ng/l, NTproBNP: 1286 pg/ml), elevated D-dimers (2,601

μg/ml), the cardiological exam not revealing any changes at this point. Neutralizing antibodies for SARS-CoV-2 were positive. Blood cultures performed during the febrile episode were negative. With all these anamnestic, clinical, and paraclinical data, we raised suspicion of PIMS with both hepatic and neurological involvement, prompting initiation of treatment with intravenous Methylprednisolone, antiplatelet and anticoagulant therapy, hepatoprotective agents, maintaining the antibiotic treatment initiated at the local level, with initially favorable evolution.

Management. Monitoring. Evolution.

The patient was hospitalized in Pediatric Clinic I for 8 weeks, during which periodic clinical and paraclinical reassessments were performed. Following the initiation of steroid anti-inflammatory therapy and symptomatic treatment, the initial evolution was favorable, with resolution of febrile spikes, rash disappearance, and improvement in general condition. However, at approximately 4 days post-admission, febrile spikes recurred accompanied by rash, which responded to antipyretics. Considering these clinical changes, laboratory tests were repeated, revealing neutropenia (0.750×10^3/μl), thrombocytopenia (66×10^3/μl), hypochromic anemia (Hgb: 8.3 g/dl, decreasing to 6.9 g/dl), mildly elevated inflammatory markers (C-reactive protein 7 mg/l), significantly elevated ferritin (3337 ng/ml), elevated lactate dehydrogenase (1654 U/L), other coagulogram changes (fibrinogen: 118 mg/dl, INR: 1.06, APTT: 19.8 sec), and elevated D-dimers (10,370 ng/ml). Suspicion of malignancy arose, prompting a bone marrow biopsy, under the cover of steroid treatment, which did not reveal atypical cellular elements. We continued steroid therapy, intravenous hepatoprotective treatment, and symptomatic management with a stable evolution. At 2 weeks post-admission, rash recurred, along with febrile spikes. Laboratory tests showed elevated inflammatory markers, persistent neutropenia, with platelets within normal limits, persistent anemia, mild coagulogram changes. A pediatric cardiology consultation was requested, and based on echocardiography, the diagnosis of coronary artery dilatation was established: left coronary artery: 2.4 mm (Z score 2.93) - dilated, remaining dilated throughout the visible echocardiographic course, right coronary artery diameter: 2.2 mm (Z score 1.67) slightly dilated, with good biventricular systolic-diastolic function. Considering all these data, the diagnosis of atypical Kawasaki disease was established, prompting initiation of immunoglobulin treatment according to the protocol, antiplatelet and anticoagulant therapy according to recommendations, with maintenance of hepatoprotective therapy.

Neurological reassessment was also performed, considering the patient's muscle hypotonia with bilateral rizomelic motor deficit, being able to lift only with assistance, these manifestations being interpreted in the context of prolonged steroid anti-inflammatory therapy. The evolution was slowly favorable both clinically and paraclinically, requiring gradual reduction of methylprednisolone doses, maintenance of anticoagulant and antiplatelet therapy, and hepatoprotective treatment. The patient was discharged after 8 weeks in good general condition, afebrile, with balanced cardiac and respiratory functions, with recommendations to continue antiplatelet treatment and periodic pediatric and cardiological reassessments.

DISCUSSIONS

KD is a systemic vasculitis commonly found in pediatric patients, particularly those under the age of 5. In developed countries, if left untreated, it becomes the predominant cause of acquired heart disease in 25% of affected children [17]. The etiopathogenesis of this disease remains incompletely understood, encompassing uncertainties about the causative agent, the immune system's role, the mechanisms driving the disease, and potential long-term consequences. PIMS is a newly identified condition that appeared during the SARS-CoV-2 pandemic [18-22]. While most children infected with SARS-CoV-2 show no symptoms, a small percentage develop PIMS, manifesting with fever, low blood pressure, digestive issuses, and heart dysfunction [22]. Initially, PIMS was termed Kawasaki-like syndrome due to mucocutaneous symptoms and other clinical and paraclinical similarities. Similarly, our patient presents both criteria corresponding to the diagnosis of PIMS, such as suggestive hereditary and collateral history (mother with respiratory illness), positive antibodies for SARS-CoV-2, elevated inflammatory markers, anemia, leukopenia, thrombocytopenia, and clinical manifestations, as well as elements that could classify it under the diagnosis of KD, namely clinical manifestations, paraclinical investigations, and cardiac involvement.

Despite the global spread of the COVID-19 pandemic, resulting in over 2.7 million deaths, children have accounted for only a small percentage (0.2%) of the infected population [23]. Mortality rates among children were reported to be low, ranging from 0.02% in 5,015 children with mild cases to 2% in 319 children with severe cases and/or preexisting chronic conditions, including obesity [24]. Nonetheless, there have been instances where groups of children developed "cardiogenic shock," characterized by a decreased left ventricular ejection fraction and elevated cardiac enzymes. They also exhibited

unusually low diastolic pressure suggestive of "toxic shock," along with other features reminiscent of KD, as described in England, Italy, France, and the USA [25].

The latest review has examined recent developments in the epidemiology, pathophysiology, clinical and biological features, as well as current treatment strategies for Pediatric Inflammatory Multisystem Syndrome (PIMS) associated with SARS-CoV-2 [26]. While SARS-CoV-2 infection in children typically manifests as mild with a low mortality rate, there is increasing recognition of Pediatric Inflammatory Multisystem Syndrome (PIMS), also known as Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19. This syndrome can lead to severe illness and long-term disabling side effects. Although PIMS shares clinical and laboratory characteristics with KD, it possesses distinct features and necessitates a clear clinical and pathophysiological definition [27]. As observed, not all children with PIMS have a positive PCR test for SARS-CoV-2 infection, PIMS occurring later, about 3-4 weeks after acute infection, being a post-infectious complication, a primary complication of SARS-CoV-2 infection [27]. There are several theories of PIMS pathophysiology, the most accepted being the dependence of the disease on IgG antibodies and the cytokine storm, with antibodies having the ability to activate monocytes leading to persistent pancytopenia and severe activation of CD8 T cells [28,29]

KD and PIMS have overlapping characteristics, as we have shown, which pose a challenge in distinguishing between the two entities. Unfortunately, there is no definitive criterion to absolutely distinguish these two pathologies, which often leads to diagnostic errors [30]. Additionally, PIMS is a relatively new entity compared to KD, so its etiology, physiopathology, diagnostic criteria, and treatment are still under research and continuous discussion. The management of this syndrome relies on KD management and other similar pathologies, highlighting the importance of further investigations to establish a rapid and accurate diagnosis with a favorable prognosis [31]. One of the criteria for PIMS reported in the studies, which in fact differentiates it from KD, is age. It has been observed that PIMS affects children aged above 9 years and young people under 21 years. These individuals typically present with persistent fever and involvement of at least two organ systems, such as gastrointestinal, hematological, mucocutaneous, respiratory, musculoskeletal, neurological, and/or renal systems [32]. Furthermore, PIMS may manifest with arterial hypotension or cardiogenic shock, along with cardiac abnormalities such as myocardial dysfunction, pericarditis, valvulopathies, or coronary anomalies. Diagnostic assessments may reveal modified echocardiographic findings and elevated cardiac enzymes like Troponin and NT-Pro BNP, as well as coagulopathy or increased D-dimers [32]. Thus, so far, we have three types of presentations of PIMS, such as persistent fever and gastrointestinal symptoms, cardiogenic shock and left ventricular dysfunction, and the third Kawasaki-like syndrome type.

PIMS may exhibit distinct features from KD, such as an onset age above 7 years and widespread cardiovascular involvement, implying a generalized immune-mediated disorder. However, the pathophysiology of PIMS remains unclear. Potential mechanisms include the recognition of antibodies or T cells to viral antigens expressed on infected cells, the formation of immune complexes that trigger inflammation, and viral superantigen sequences that activate host immune cells. Most COVID-19-associated PIMS cases have been managed using standard KD protocols. In patients with cardiac dysfunction and arterial hypotension, inotropic and vasoactive agents are often necessary, and anticoagulants are frequently used. However, the medium and long-term outcomes of PIMS, such as the risk of coronary aneurysm formation, are still uncertain and necessitate ongoing careful monitoring [33].

Most children with COVID-19 remain asymptomatic, with fewer than 10% needing hospitalization, and only 2 out of 100,000 developing PIMS. Nonetheless, it is crucial to remain alert when a child or adolescent presents with persistent fever, particularly if they have a history of SARS-CoV-2 infection. Both PIMS and KD are hiperinflammatory conditions that can affect the cardiovascular system, but PIMS is directly linked to the SARS-CoV-2 viral illness [34].

CONCLUSIONS

In conclusion, we are currently facing two similar yet distinct entities, and the differences between them are subtle and often challenging, especially in the absence of a defining criterion for PIMS, the newly emerged entity. Over time and in multiple studies, notable differences between KD and PIMS have been found to be related to age, geographic area, and clinical manifestations. PIMS is more common in Europe and North and South America, while KD is more frequently encountered in Asia. Clinical manifestations, such as fever duration, also differ between the two conditions. Treatment and management approaches may also have subtle variations. It is important to recognize PIMS as quickly as possible to ensure correct management and monitor long-term complications, as this condition can be life-threatening.

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