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Diagnostic challenges in the pediatric inflammatory multisystem syndrome (PIMS/MIS-C) in a 6-year-old boy: a case report

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A. Study design/planning
B. Data collection/entry
C. Data analysis/statistics
D. Data interpretation
E. Preparation of manuscript
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G. Funds collection

Abstract

Pediatric Inflammatory Multisystem Syndrome (PIMS), or Multisystem Inflammatory Syndrome in Children (MIS-C), is a severe systemic inflammatory condition in children often occurring after asymptomatic SARS-CoV-2 infection. It is life-threatening, characterized by high fever (>38.5°C), and multisystem inflammation. Symptoms include severe abdominal pain, chest pain, arrhythmias, rash, and conjunctivitis. Laboratory findings typically show elevated inflammatory markers, coagulation abnormalities, and cardiac damage. Treatment involves immunoglobulins, glucocorticoids, and biological medicines to suppress immune hyperactivity, reducing inflammation and protecting organ function. PIMS/MIS-C has gained attention in the post-COVID-19 era, with an incidence of 2-5 cases per 100,000 children globally and 4 per 100,000 in Poland. Early recognition is crucial to mitigate severe outcomes. The report discusses a 6-year-old male presenting with high fever, abdominal pain, and rash, alongside laboratory evidence of inflammation and coagulopathy. Differential diagnoses included Kawasaki disease, septic shock, and toxic shock syndrome. Treatment followed the WHO guidelines, including immunoglobulins, glucocorticoids, and acetylsalicylic acid. Timely intervention prevented complications such as coronary aneurysms and myocardial dysfunction. Continued research and education are essential to enhance diagnostic and therapeutic strategies.

Keywords: MIS-C, SARS-CoV-2, PIMS, inflammation, treatment

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Introduction

Pediatric Inflammatory Multisystem Syndrome (PIMS), otherwise known as Multisystem inflammatory syndrome in children (MIS-C) is a severe, life-threatening systemic inflammatory disease of acute onset. It is

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estimated to occur with a prevalence of 1/3000 in children infected with the recent, often asymptomatic SARS-CoV-2 virus [1]. It is characterized by fever, usually above 38.5°C, and symptoms of multi-organ damage: severe abdominal pain, chest pain, cardiac arrhythmias, rash, conjunctivitis. In severe forms, there is damage to the heart muscle and other organs and even death. Pooled analysis has shown that approximately 20% of children with MIS-C develop acute kidney injury [2]. Laboratory findings include lymphopenia, thrombocytopenia, elevations in C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), procalcitonin, LDH, ferritin or D-dimers. Treatment is based on the use of immunoglobulins, glucocorticosteroids, and biologic drugs to suppress the inflammatory response. The first-line drug used is intravenous immunoglobulin (IVIG), while methylprednisolone is the second-line treatment. As a last resort, biologic drugs (IL-1 antagonists, IL-6 receptor blockers or anti-TNF drugs) can be used [3].

Case description

A six-year-old boy, in an average general condition, was admitted to the Pediatric Department due to high fever, severe abdominal pain and vomiting (body weight: 17 kilograms (3^{rd}-10^{th} percentile), height: 112 centimeters (10^{th} percentile), Body Mass Index (BMI): 13.55 (3^{rd}-10^{th} percentile)) (Figure 1). Vital signs were within normal limits, only an elevated blood pressure of 140/81 mmHg attracted attention. The history showed that the boy, two weeks before hospitalization, had undergone a rhinitis infection, had been unsuccessfully treated with clarithromycin. Having completed the antibiotic therapy, the boy started having a fever again and reported abdominal pain. Laboratory tests performed on admission showed leukocytosis: 38.000/ul (normal: 4.500-14.500/ul) and high inflammatory markers CRP: 53.1 mg/l (normal: <5 mg/L), PCT: 1.36 ng/ml (normal: <0.05 ng/ml), elevated fibrinogen: 5.81 g/l (normal: 1.8-3.5 g/l) and ketones in urine: 7.8 mmol/l (normal: <0.5 mmol/l). The absence of *Mycoplasma pneumoniae* infection was confirmed through negative PCR results and serological tests. Adenovirus, influenza viruses A and B, RSV and SARS CoV-2 were excluded by an antigen test. In view of the laboratory results and the child's distressing condition, third-generation cephalosporins were initially included in the treatment, without resolution of the fever. ECG was without abnormalities. UKG, abdominal CT scan did not show any abnormalities (Table 1). Blood, urine and stool cultures were negative, but ANA-1 antinuclear antibodies were positive.

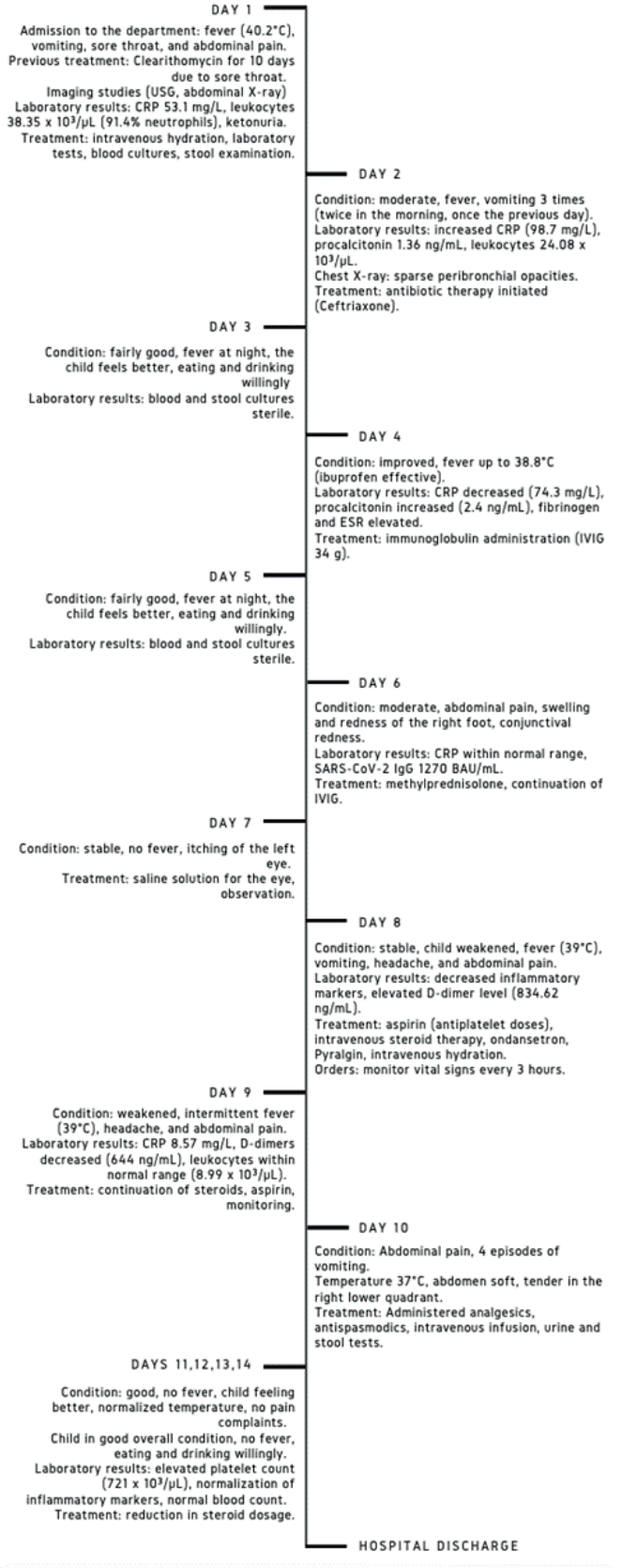


Figure 1. Treatment history

Table 1. Descriptions of additional tests

UKG	The heart chambers are proportionate and not enlarged. The aortic valve is tricuspid, with coronary arteries originating in typical locations. The tricuspid valve (TV) is competent; pulmonary valve (PV) shows trace regurgitation, within normal limits; mitral valve (MV) is competent, E/A ratio is 1.6. Flows across the atrioventricular valves and arterial trunks are normal. No pericardial abnormalities. No arrhythmias were detected during the examination. Ejection fraction (EF) is 67%, aortic valve velocity (VAo) is 1.19 m/sec. No features of congenital heart defects.
Abdominal CT	Mesenteric lymph nodes up to 4-5 mm in the short axis. The gallbladder has smooth walls. Extrahepatic and intrahepatic bile ducts are not dilated. The liver is enlarged, approximately 12 cm in the midclavicular line. The pancreas is not enlarged. The Wirsung duct is not dilated. The spleen is approximately 10 cm in the long axis. The adrenal glands are not enlarged. Both kidneys are normal. The urinary bladder has smooth, thin walls. Large abdominal vessels are not dilated.

On the fifth day of hospitalization, the boy developed redness of the conjunctiva and tongue and enlarged lymph nodes. Conjunctivitis is in the case a unique clinical feature that may suggest the diagnosis (criteria for the diagnosis of the disease are presented in Table 2). Taking into account the overall picture and the results of the investigations, PIMS/MIS-C syndrome was suspected – the level of anti-SARS-CoV-2 antibodies determined was high at 1260 BAU/ml. Immunoglobulin, steroid therapy and ASA were included in the treatment, with a gradual improvement in the patient's general condition.

Table 2. Criteria for the diagnosis of MIS-C according to the World Health Organization

Children and adolescents aged 0-19 years with fever > 3 days	
Clinical features	Two of the following: 1) rash or bilateral non-purulent conjunctivitis or signs of mucositis and dermatitis (in the mouth, hands or feet), 2) hypotension or shock, 3) evidence of myocardial dysfunction, pericarditis, valvular inflammation or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP levels), 4) evidence of coagulopathy (on PT, PTT, elevated D-dimers), 5) acute gastrointestinal problems (diarrhea, vomiting or abdominal pain)
Inflammatory markers	Elevated inflammatory markers such as ESR, C-reactive protein or procalcitonin
Absence of other etiology	No other obvious microbial causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes
Evidence of COVID-19	Evidence of COVID-19 virus (RT-PCR, antigenic test result or positive serology) Likely contact with COVID-19 patients

Notes: Own elaboration based on the WHO's data [4].

In order to diagnose PIMS, it is essential that the first five criteria are met. The requirements constitute a mandatory set of conditions that must be met to establish a diagnosis. In situations where there is a significant suspicion of PIMS, criterion number 6 may be considered optional. In other words, in cases strongly suggestive of PIMS, failure to meet the sixth criterion does not rule out the diagnosis, provided that all other conditions (1 to 5) are consistent with the observed symptoms and findings. The case described corresponds adequately to all the criteria defined in Table 2. The analysis of the individual conditions begins with the patient's age, which is 6 years. Next, fever is observed.

Laboratory evidence of elevated inflammatory markers including C-reactive protein (CRP), procalcitonin (PCT), red blood cell sedimentation rate (ESR) and fibrinogen was confirmed. Clinical signs included severe abdominal pain and vomiting. Other causes that could explain the present symptoms were excluded, which reinforces the accuracy of the diagnosis. Finally, the association with COVID-19 infection was confirmed by the presence of specific antibodies, which completes the clinical picture and allows the described case to be clearly assigned to the criteria in Table 2.

Case analysis

MIS-C, also known as PIMS, is a rare but serious condition associated with SARS-CoV-2 infection. The exact pathogenesis is unclear, but genetic predispositions and environmental factors are believed to influence susceptibility and severity. Research indicates higher risks in certain ethnic groups. A study in *Frontiers in Pediatrics* reported that Black children have a 15-fold and Asian children an 11-fold increased risk of developing MIS-C, as compared to White children after SARS-CoV-2 infection [5]. It suggests that genetic factors may contribute to the disparities. Similarities between MIS-C and Kawasaki disease (KD), another hyperinflammatory condition with genetic predispositions, further support a genetic basis for MIS-C susceptibility [6]. Environmental factors, including crowded living conditions, limited healthcare access, and greater exposure to pathogens, may also play a role. The socioeconomic determinants, combined with genetic predispositions, likely contribute to the increased incidence of MIS-C in specific populations.

The occurrence of non-full-blown PIMS/MIS-C can cause diagnostic difficulties. It requires differentiation from severe bacterial infections, viral infections and infections of undetermined etiology, as in KD (Table 3), there is no test to distinguish KD from MIS-C. As in KD, immunosuppressive and immunomodulatory drugs are used for treatment, based on the latest guidelines. First-line treatment is intravenous infusion of immunoglobulin – IVIG, at a dose of 2.0 g/kg. Second-line therapy (administration of methylprednisolone: 10-30 mg/kg, i.v.) should be considered when: the child's condition worsens within 24 hours after IVIG, coronary artery aneurysms are present on the Ultrasound Cardiography examination, the child is <12 months of age, presents features of shock. Additionally, the use of IVIG in combination with glucocorticoids has been shown to be beneficial, as compared to IVIG alone. When high-dose steroids are used, it is important to remember to include PPI drugs (e.g. omeprazole) in the treatment to protect the stomach. In refractory cases, third-line therapy is used. It constitutes biological therapy: anakinra (IL-1 antagonist), tocilizumab (IL-6 receptor blockers) and infliximab (TNF-alpha inhibitor) [4]. Due to the deterioration of the child's condition, it was decided to administer a single dose of methylprednisolone at 20 mg, followed by the initiation of IVIG infusions an hour later (a total of 34 g was administered during the treatment process), resulting in an improvement in the clinical condition.

Table 3. Comparison of features of PIMS and KD

Comparative feature	PIMS	Kawasaki disease
Age group	Typically affects school-age children (5-14 years old).	Mostly affects infants and toddlers (6 months to 5 years old).
Gender	Mainly men	Mainly men
Race	African-Americans, Hispanics	Asians
Etiology	Post COVID-19 syndrome, positive serology or contact with an infected person	Cause cannot be identified

Comparative feature	PIMS	Kawasaki disease
Clinical onset	Occurs 2-6 weeks after SARS-CoV-2 infection or exposure.	Acute onset without a clear preceding infection
Intensive care support on admission	>50% (hemodynamic instability)	Approximately 5%
Multi-organ dysfunction	Common	Usually no
Cardiac involvement	Frequent, including myocarditis, pericarditis, and shock	Coronary artery aneurysms are common complications
Gastrointestinal symptoms	Common: abdominal pain, diarrhea, vomiting	Rare: mild gastrointestinal symptoms may occur
Rash and mucosal changes	Variable rash; conjunctivitis and mucosal changes may occur	Characteristic polymorphic rash, "strawberry tongue", and cracked lips
Lymphocyte count	Decreased	Correct
Ferritin concentration	Increased	Correct
Troponin I concentration	Increased	Correct
CRP	Significantly increased	Moderately increased
Therapy	IVIG, GCS, IL-1 antagonists, IL-6 receptor blockers anti-TNF drugs	IVIG, GCS, IL-1 antagonists
Prognosis	Good with prompt treatment, though risk of long-term cardiac issues	Generally good, but risk of coronary artery complications

Notes: Own elaboration based on Zhang et al. [7].

PIMS can lead to complications such as coronary artery aneurysms, which occur in 10-20% of hospitalized children. The frequency of their detection depends on the effectiveness and frequency of echocardiograms, which are necessary both during the acute phase of the disease and in the recovery period. Whittaker et al. demonstrated that aneurysms can occur independently of inflammation and cardiac muscle damage markers [8]. Another complication is heart dysfunction. Children with PIMS may experience transient reductions in left ventricular ejection fraction. Despite full clinical recovery, echocardiographic changes may persist for several months after the illness, sometimes remaining permanent [9]. PIMS-related complications highlight the need for regular specialist care, including cardiology, as well as adherence to medical recommendations and follow-up tests.

Conclusions

Although PIMS/MIS-C is a fairly rare complication of COVID-19, with an initial incidence estimated at 45-54 cases per 100,000 cases (data for children under 15 years of age for the Italian population), long-term follow-up of the patient is crucial for early detection and prevention of complications that may represent a life-threatening condition [10]. A cardiac follow-up 2-4 weeks after discharge from hospital, at which an Electrocardiogram and Ultrasound Cardiography are performed, is recommended.

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