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ORIGINAL PAPER

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Clinical profile and management of patients with pediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 – single-center experience

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ABSTRACT

Introduction and aim. Pediatric Inflammatory Multisystem Syndrome (PIMS-TS) is a new condition that has emerged in children during the COVID-19 pandemic. Many clinical signs and symptoms resemble those found in Kawasaki disease (KD).

Material and methods. The following data were considered: clinical presentation, comorbidities, laboratory findings, abnormalities in additional tests, exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the child and his family members, applied treatment and return to full health.

Results. In the presented study nineteen children were analyzed. Fever was a universal finding in our group and it's mean duration was 7 days (range 5-9). Other common symptoms included abdominal pain and severe weakness (in 89.5%), rash and conjunctivitis (in 84.2%), vomiting (in 73.7%) and mucous membrane involvement (in 63.2%). In nearly half of cases, echocardiography revealed fluid in the pericardial sac and left ventricular systolic dysfunction (in 52.6% and 47.4% respectively). 21.1% of patients had coronary artery abnormalities. 26,3% of the children required treatment with dopamine and/or milrinone. In 15.7% ICU admissions and assisted ventilation was necessary. No deaths were recorded.

Conclusion. One should bear in mind that PIMS-TS can mimic KD, appendicitis and meningitis, which may pose a diagnostic challenge.

Keywords. COVID-19, KawaCOVID, Kawasaki disease PIMS-TS, MIS-C, SISCoV

The list of abbreviations: **PIMS-TS/MIS-C** – Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, **KD** – Kawasaki Disease, **CI** – confidence interval, **ICU** – Intensive Care Unit, **IVIG** – intravenous immunoglobulin, **PCT** – procalcitonin, **CRP** – C-reactive protein, **WHO** – World Health Organization, **CDC** – Centers for Disease Control and Prevention

Introduction

Pediatric inflammatory multisystem syndrome temporarily associated with COVID-19 (PIMS-TS), also known as a multisystem inflammatory syndrome in children (MIS-C), systemic inflammatory syndrome in COVID-19 (SISCoV), pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (KawaCOVID), is a new condition that has emerged in children during

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the COVID-19 pandemic.[1-3] In early 2020, it was expected that children will be the least affected population in terms of morbidity and mortality associated with COVID-19.[4] However, since April 2020 researchers mainly from Europe and the United States have reported many cases of severely unwell children presenting with Kawasaki disease-like features. Its regional incidence correlated with the frequency of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Although, the incidence peaks were shifted by 2-6 weeks.[5,6] Most children met the genetic or serological criteria for SARS-CoV-2 infection.[7,8]

It is suggested that PIMS-TS results from dysregulation of the immune response to the SARS-CoV-2 infection. Many clinical signs and symptoms resemble those found in Kawasaki Disease (KD). These include systemic inflammation, persistent fever, rash, mucositis, conjunctivitis and cardiac involvement.[9] Despite those similarities, recent studies suggest that distinct inflammatory pathways are involved in the pathogenesis of KD and PIMS-TS.[10-14] In addition, patients with PIMS-TS are older, more often complain of gastrointestinal symptoms and present with features of heart failure, in comparison to children with KD. They also more frequently require Intensive Care Unit (ICU) admission, as well as cardiovascular and respiratory support.[15,16] The incidence of both entities differ in various regions around the world – most cases of KD are diagnosed in children of Asian origin, whereas PIMS-TS affects primarily patients of African, Afro-Caribbean, and Hispanic descent.[8,17]

Aim

The aim of the article was to present the clinical characteristics and management of children diagnosed with PIMS-TS. In addition, we wanted to find out the differences between the previously known and having similar features, KD and draw attention to possible difficulties in diagnosing this disease, the cases of which will continue to appear in connection with the ongoing global COVID-19 pandemic.

Material and methods

Our work is a retrospective case series study carried out in the Department of Pediatrics of the State Hospital in Rzeszów, Poland. Nineteen cases of children diagnosed with PIMS-TS were analyzed between November 15, 2020, and January 2, 2021. The diagnosis was made according to the case definitions presented in WHO and CDC publications: persistent fever, elevated inflammatory markers, features of multi-organ dysfunction, epidemiologic link to SARS-CoV-2 infection, and exclusion of other viral and bacterial pathogens as the cause of inflammation.[18,19]

The following data were collected: clinical presentation, comorbidities, laboratory findings (parameters of inflammation, blood count with smear, parameters of cardiomyocyte damage, kidney damage, coagulation, nutrition, transaminase, electrolytes), abnormalities in imaging examinations (chest X-ray, ultrasonography, echocardiography), exposure to SARS-CoV-2 (presence of antibodies against the disease in a child, confirmed/probable infection in the last weeks in one of the child's family members), applied treatment (immunoglobulin infusions, administration of glucocorticosteroids, positive inotropic agents and antithrombotic therapy), the need to stay in the ICU and return to full health.

Results are presented as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data.

Ethical approval was obtained from the Bioethics Committee at University of Rzeszow (resolution 9/01/2021).

Results

The median age of the patients was 8.3 years (5.3–9.6 IQR). All cases occurred in the period from November 15, 2020, to January 2, 2021. All children were Caucasian. 42.1% of cases were female. In 3 children (15.7%) the following diseases coexisted: bronchial asthma, overweight or obesity. No other comorbidities were reported.

The entire group of 19 children was tested for active infection with the SARS-CoV-2 virus (a genetic test for RNA detection from a nasopharyngeal swab or an antigen test) and all were negative. The level of SARS-COV-2 IgG antibodies were determined in 18 patients. Their positive result was obtained in 17 out of 18 (94.4%) cases. The mother of the patient whose SARS-CoV-2 antibody level was not marked had COVID-19 infection confirmed by genetic testing 4 weeks earlier.

Out of 18 interviewed families, 13 (72.2%) reported symptoms of respiratory tract infection in a close family member of the child 4-6 weeks before hospitalization. However, only 5 out of 19 (26.3%) patients reported such symptoms at similar time.

Clinical characteristics

The mean duration of the fever was 7 days (range 5-9). Other common symptoms included abdominal pain and severe weakness (in 89.5% of cases), rash and conjunctivitis (in 84.2%), vomiting (in 73.7%) and mucous membrane involvement (in 63.2%). Hypotension, diarrhea, hyperesthesia and headache were observed in half of the children. The summary of the clinical presentations is shown in Table 1.

Our study group included a few patients with a clinical picture of the disease suggesting a different diagnosis. Persistent headache, impaired consciousness and hyperestesia were predominant in one patient. Due to

symptoms suggestive of meningitis, this child underwent a head Computed Tomography scan and lumbar puncture which showed no abnormalities. The second child presented with clinical and sonographic symptoms suggestive of appendicitis. Appendectomy was performed but no significant changes were found on histopathology. Another patient with pyuria and kidney oedema on ultrasound was initially diagnosed with pyelonephritis. Subsequently, when despite the antibiotic therapy new symptoms developed, the PIMS-TS diagnosis was established.

Table 1. Clinical presentation

	Number of patients/19 (%)
Fever	19/19 (100)
Cervical lymphadenopathy	6/19 (31.6)
Gastrointestinal symptoms: - abdominal pain - vomiting - diarrhoea	 17/19 (89.5) 14/19 (73.7) 10/19 (52.6)
Dermatological and mucosal symptoms: - rash - swollen hands/feet - conjunctivitis - red lips/strawberry tongue - peeling of the skin	 16/19 (84.2) 8/19 (42.1) 16/19 (84.2) 12/19 (63.2) 5/19 (26.3)
Cardiovascular symptoms: - hypotension - arrhythmia/bradycardia	 10/19 (52.6) 3/18 (15.8)
Respiratory symptoms - dyspnea - cough	 7/19 (36.8) 2/19 (10.5)
Neurological symptoms: - hyperesthesia - headache - confusion - photophobia	 9/19 (47.4) 9/19 (47.4) 3/19 (15.8) 5/19 (26.3)
Physical weakness	17/19 (89.5)
Petechiae	2/19 (10.5)
Swollen eyelids	4/19 (21.2)
Myalgia	4/19 (21.2)

Laboratory investigations

The highest level of inflammatory parameters was recorded on average on the 6.0 day (range 4-9) of the fever. Increased levels of CRP, D-dimers and NT-proBNP were found in all children, elevated PCT in 17 (89.5%) patients. A notable number of patients had elevated fibrinogen, ferritin and cardiac troponin levels. Abnormalities in platelet count (thrombocytopenia on admission and thrombocytosis observed later during hospitalization), anaemia, lymphopenia, neutrophilia, hypoproteinemia and hypoalbuminemia were also noticed. A detailed list of all laboratory investigations is included in Table 2.

Table 2. Laboratory findings – most abnormal level during hospitalization

	Reference value	**Abnormal n/ total (%)**	**Median (IQR)**
Leukocytes max	4.5–13.5 [10^3/µl]	7/19 (36.8)	11.8 (10.4 – 15.7)
Leukocytes min	4.5 – 13.5 [10^3/µl]	4/19 (21.1)	6.5 (5.2 – 8.3)
Granulocytes max	1 – 8.0 [10^3/µl]	11/19 (57.9)	8.4 (4.7 – 12.2)
Lymphocytes min	1.5 – 5.0 [10^3/µl]	12/19 (63.2)	1 (0.5 – 1.6)
Thrombocytes min	180 – 450 [10^3/µl]	13/19 (68.4)	144.5 (112.5 – 188)
Thrombocytes max	180 – 450 [10^3/µl]	8/19 (42.1)	398 (314 – 722)
Haemoglobin min	11.5 – 14.5 [g/dl]	16/19 (84.2)	9.7 (8.9 – 10.7)
CRP	<10 [mg/l]	19/19 (100)	183.1 (105.1 – 240.7)
PCT	<0.5 [ng/ml]	17/19 (89.5)	3.1 (1 – 11.4)
Ferritin	22 – 322 [ug/l]	10/18 (55.6)	407.1 (183.9 – 543)
Nt-proBNP	<125 [pg/ml]	19/19 (100)	5 878 (2 316.5 – 16 762.5)
Troponin T	<2,5 [ng/l]	11/19 (57.9)	288.4 (182.9 – 433.7)
D-dimers	<500 [ng/ml]	19/19 (100)	6 839 (3 115.5 – 11 369)
Fibrinogen	2 – 4 [g/l]	14/17(82.4)	5 (4 – 7.1)
Serum sodium min.	136 – 145 [mmol/l]	15/19 (78.9)	133.0 (131.5 – 134)
Serum calcium min.	9.12 – 10.2 [mg/dl]	16/19 (84.2)	8.1 (7.4 – 8.8)
Albumin min.	3.5 – 5.6 [g/dl]	12/19 (63.2)	3.1 (2.6 – 3.7)
Protein	6.8 – 8.0 [g/dl]	17/19 (89.5)	5.7 (5 – 6.1)
INR	0.85 – 1.2	11/16 (68.8)	1.3 (1.2 – 1.4)
APTT	24 – 36 [s]	9/15 (60)	37.2 (32.8 – 38.4)

Depending on the marking: max – the highest recorded value, min – the lowest recorded value and with no designation the maximum value, INR – international normalized ratio, APTT – activated partial thromboplastin time, IQR – interquartile range

Chest X-ray and ultrasonography

Chest X-rays were performed in 18 patients – in 8 (44.4%) inflammatory changes were found. In almost all of these cases, the pleural fluid was additionally visualized using ultrasound. One child with a normal radiograph showed isolated fluid in the pleural cavities. In 5 (26.3%) children, due to clinical indications, CT of the chest was additionally performed – in 4 cases pulmonary parenchyma involvement was visible.

Abdominal ultrasound was performed in 17 (89.4%) patients. 12 of them had some abnormalities, including images of acute appendicitis, swelling of the intestinal wall, mesenteric lymphadenopathy, abnormal image of the gallbladder, hepato- or splenomegaly and free fluid (which was the most common sign seen in nearly half of cases). In one child, abdominal ultrasound detected features of liver damage (correspond with the clinical status and laboratory tests), another patient had an abnormal kidney image – the obliteration of the corticomedullary differentiation. Table 3 and 4 shows in detail abnormalities found on the ultrasound examination.

Table 3. Abdominal ultrasound findings (n=17)

	Number of patients (%)
Ascites	8 (47.1)
Mesenteric lymphadenitis	5 (29.4)
Hepato/splenomegaly	5 (29.4)
Bowel wall thickening	3 (17.6)
Abnormal image of the gallbladder	2 (11.8)
Changes suggestive of acute appendicitis	2(11.8)

Table 4. Chest ultrasound findings (n=9)

	Number of patients (%)
Pleural fluid	8/9 (88.9)
Subpleural consolidations	4/9 (44.4)

Echocardiography

Each patient underwent echocardiography. The most common deviation present in nearly half of children were fluid in the pericardial sac and left ventricular systolic dysfunction (in 52.6 and 47.4% respectively). 21.1% of patients had coronary artery abnormalities: dilatation of the left coronary artery in two children (in one of them with a visible hyperechoic wall), and of the right coronary artery in the other two. Table 5 presents characteristics of the echocardiography findings.

Treatment

All children were treated with intravenous immunoglobulin infusion (IVIG) – 2 of them were given a dose of 1 g/kg, 13 – 2 g/kg and 4 received 4 g/kg. Glucocorticosteroids pulses and/or an additional dose of 2 g/kg IVIG was administered due to the lack or partial response of first line treatment (IVIG alone). Indications for escalation of treatment were: severe or worsening general condition of the child, features of shock, persistent fever 24-36 hours after the end of the IVIG infusion or its relapse.[17] Patients had the implemented treatment on an average of 5.5 days (range 4-7 day) since the onset of the fever and after an average of 2.5 (range 1-5) days of hospitalization.

Table 5. Echocardiography abnormalities (n=19)

	Number of patients (%)
Pericardial effusion	10 (52.6)
Left ventricular dysfunction	9 (47.4)
Mitral valve regurgitation	6 (31.6)
Tricuspid regurgitation	4 (21.1)
Coronary artery dilation	4 (21.1)
Enlarged left chamber	2 (10.5)
Enlarged right chamber	1 (5.3)

Intravenous methylprednisolone pulse therapy at the daily dose of 20 mg/kg for 3 days followed by 2 mg/kg/day was additionally administered in over half of the patients.[20,21] It was given on average after another 24 hours of having a fever (in 5-8 day of fever). Two (10.5%) children received 2 mg/kg/day methylprednisolone from the start of hospitalization. By the time of discharge, patients were transitioned to an equivalent dose of oral prednisone and then tapered off over two to three weeks. In one case steroid therapy was complicated by steroid-induced hyperglycemia.

Five (26.3%) children had symptoms of shock and had to be treated with dopamine and/or milrinone. Passive oxygen therapy was used in 5 children (26.3%), 3 of which required treatment in the ICU and assisted ventilation – high flow nasal cannula.

All children received antithrombotic treatment. Enoxaparin (at a dose of 1 mg/kg) and acetylsalicylic acid (at a dose of 3-5 mg/kg or 30-50 mg/kg in the case of coronary arterial involvement) were used. Table 6 presents the characteristics of the applied treatment.

Table 6. Applied treatment (n=19)

	Number of patients (%)
IVIG	19 (100)
Pulses of methylprednisolone	11 (57.9)
Dopamine and/or milrinone	5 (26.3)
Cephalosporins II/III generation	19 (100)
Another antibiotic	6 (31.6)
Betablokers	4 (21.1)
Enoxaparin	8 (42.1)
Aspirin	14 (73.7)
Furosemide	9 (47.4)
Albumin	2 (10.5)

The mean hospitalization length was 12 days (range 8-18). All children were discharged in good general condition (no symptoms, with normal echocardiography results). Only 2 patients had sinus bradycardia, the rest recovered without sequelae. No deaths were recorded.

Discussion

In the last weeks of 2020 pediatricians in our region were overwhelmed by a large number of seriously ill children with PIMS-TS. Within several weeks, children suspected of this disease were admitted to the hospital almost every day, some of whom required oxygen treatment and/or intensive care. As in other regions of the world, the rise in the number of PIMS-TS cases was preceded by a wave of SARS-COV2 infections. In our region, the increased wave of SARS-COV2 infections was delayed but it arrived with high intensity in the fall of 2020.

As it is emphasized in the previous reports the clinical picture of PIMS-TS overlaps with the symptoms present in KD. In both diseases, it can be observed multiform rash, mucosal symptoms, conjunctivitis, cervical lymphadenopathy, and hand/foot swelling. However less than 50% of children with final diagnosis of PIMS-TS meet clinical criteria for the diagnosis of KD.[22] In PIMS-TS the most common complication in the cardiovascular system is left ventricular systolic dysfunction, in KD it is dilatation/aneurysm of the coronary arteries.[23-26,34]

Symptoms of shock are more common in subjects with PIMS-TS, while similar life threatening symptoms are reported in less than 10% of children with KD (Kawasaki shock syndrome).[23,27] Gastrointestinal and neurological symptoms are undoubtedly more common in PIMS-TS.[28] Due to the frequent occurrence of gastrointestinal symptoms, especially severe abdominal pain, PIMS-TS may resemble acute appendicitis or enteritis.[29] Frequent neurological symptoms may raise the suspicion of neuro infection.[30] Due to a diverse clinical picture, the differential diagnosis of PIMS-TS is extensive and the correct diagnosis is often difficult.

In children diagnosed with PIMS-TS, increased concentrations of CRP, PCT, ferritin, D-dimers, fibrinogen, troponin, Nt-proBNP are observed. Hypoalbuminemia, anaemia, thrombocytopenia, neutrophilia and lymphopenia are commonly detected. The same laboratory abnormalities occur in KD, however, lower levels of inflammatory parameters and myocardial injury markers as well as higher leukocytes and platelets counts are found.[31,32] Both, in KD and in PIMS-TS, high serum PCT concentrations are detected. This parameter is considered to be a marker of systemic bacterial infection, while no bacterial infection can be found in both of these diseases. Probably the high PCT is the result of uncontrolled and excessive release of pro-inflammatory cytokines - a cytokine storm.[33,34]

Because the clinical picture of PIMS-TS has some similarities to KD, similar treatment methods are used.[35] All children in presented group received immunoglobulin infusions, majority were treated with intravenous corticosteroids. Intravenous antibiotic therapy was administered in all cases, until the results of negative microbiological tests (blood, urine, rectal smear culture) were obtained, which, according to the previously mentioned WHO and CDC criteria, allowed the diagnosis to be confirmed.

Conclusion

In summary, the reported group of children with PIMS-TS presented similar features as previously described. Due to the multitude of possible clinical symptoms, PIMS-TS can mimic KD, appendicitis, meningitis and other disease entities characterized by a systemic inflammatory response. It may also coexist with other diseases. Because of the overlapping clinical manifestations between PIMS-TS and KD, patients with PIMS-TS are treated with the therapeutic protocols used in KD. Further research is needed to establish the optimal therapeutic approach to a child with PIMS-TS.

Declarations

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Author contributions

Conceptualization, P.O.Z., P.M., K.P. and B.K.; Methodology, P.O.Z. and B.K.; Software, P.O.Z.; Validation, P.O.Z.; Formal Analysis, P.O.Z.; Investigation, P.M. and K.P.; Resources, P.M. and K.P.; Data Curation, K.P. and B.K.; Writing – Original Draft Preparation, P.O.Z., K.W. and B.K.; Writing – Review & Editing, P.O.Z.; Visualization, P.O.Z.; Supervision, K.P. and B.K..; Project Administration, P.O.Z.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

Ethics approval

Bioethics Committee at University of Rzeszow (resolution 9/01/2021).

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