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CASE REPORT

Well-known symptoms, new disease – a case of SARS-CoV-2 infection in an eight-year-old boy

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ABSTRACT

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) is a new disease in children, connected with the COVID-19 pandemic. The main cause of this disease is dysregulation of the immune homeostasis.

We report the first case of PIMS-TS in the Polish Mother's Memorial Hospital Research Institute in Lodz. Many non-specific symptoms presented by the patient were the cause of the primary care physician's therapeutic failure, which resulted in the boy being transferred to the district hospital and then to the institute in Lodz. During the complex diagnostic process anti-SARS-CoV-2 antibodies in the IgM and IgG classes were detected. The initial diagnosis of PIMS-TS was made, and treatment with immunoglobulins and acetylsalicylic acid was initiated. The patient's condition improved the following day.

The aim of this report is to emphasize that typical symptoms do not always determine known disease entities, and to point out the need to constantly improve one's knowledge.

KEY WORDS:

acetylsalicylic acid, intravenous immunoglobulins, paediatric inflammatory multisystem syndrome associated with SARS-CoV-2 infection, disease associated with SARS-CoV-2 infection.

INTRODUCTION

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) is a new disease in children. The first reported case of PIMS-TS occurred in the USA on 7 April 2020 [1], while in Poland that novel diagnosis was confirmed almost a month later in a 2-year-old boy. Research shows that PIMS-TS is more prevalent in school-aged children with the median age of 9 years and occurs about 4 weeks after COVID-19 infection. The main cause of this disease is dysregulation of immune homeostasis. Clinical presentations include fever, cardiac involvement, gastro-intestinal symptoms, mucocutaneous manifestations, haematological features, or other organ dysfunctions.

CASE REPORT

We report an 8-year-old boy with allergy to dust mites, with no other chronic diseases, weight at the 25th percentile, and height at the 75th percentile for age. He was vaccinated in accordance with Polish recommendations.

The history of our patient starts at the primary care physician, where he reported with abdominal pain (without abnormal masses, exacerbate during movement) and 38-40^{o}C fever lasting for 4 days, of unknown origin. There he was treated with trimethoprim/sulfamethoxazole without result and then referred to the district hospital. The following treatment (ceftriaxone, fluconazole, ibuprofen, paracetamol) was administered with no improvement. Additionally, a generalized rash occurred, which

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was the reason for his transfer the patient to the Polish Mother's Memorial Hospital Research Institute in Lodz.

On admission the patchy and itchy rash (especially on the chest, lumbar area, and extremities), swelling and redness of the scrotum, auricles, and lips, "strawberry" tongue, bilateral non-purulent conjunctivitis, and enlarged anterior cervical lymph nodes were observed. The boy was weak and without appetite.

Laboratory tests showed high inflammatory markers, neutrophilia, hypoalbuminaemia, hiperferritinaemia, LDH, D-dimers, prolonged PT and INR, and high NT-proBNP. Interleukin 6 level (as an indicator of the risk of a cytokine storm) proved to be elevated (Tables 1 and 2).

Initially, the treatment was based on third-generation cephalosporin, antipyretic drugs, and intravenous fluids.

The following day, oliguria appeared. Daily protein loss in urine (1800 mg) met the criteria for nephrotic proteinuria. Systematic measurements of body weight, vital parameters, and daily fluid balance were carried out. According to the boy's increase of weight, the decision about fluid deprivation was made.

Thoracic ultrasonography revealed features of pneumonia and pleuritis with collection of fluid (55 ml) in the right pleural cavity. Echocardiography showed decreased ejection fraction of the left ventricle (56-58%). During hospitalization the boy's blood pressure was measured regularly; the lowest level was 87/44 mmHg.

Anti-Sars-CoV-2 antibodies in the IgM and IgG classes were detected.

Clinical features, laboratory results, and imaging studies led to a diagnosis of PIMS-TS.

The treatment with 2 g/kg intravenous immunoglobulins in 2 divided doses were initiated in premedication with clemastine and methylprednisolone. Acetylsalicylic acid was added. After modifying the treatment, the patient's condition improved the next day. Diuresis increased from 200 ml to 1800 ml per day (weight decreased by 1.1 kilograms). The fever, abdominal pain, and rash gradually normalized.

Due to the negative bacterial cultures, ceftriaxone was discontinued. The control echocardiography did not show significant changes.

TABLE 1. Evolution of laboratory parameters during hospitalisation

Type of test		Reference range	1st day	4th day	10th day
Blood count	HGB [g/dl] RBC [10^6/µl] PLT [10^3/µl]	12.0-15.5 4.5-5.5 150-400	11.1 4.0 140	10.0 3.5 443	12.2 4.4 675
Inflammatory markers	CRP [mg/dl] PCT [ng/ml] D-dimers [ng/ml] Ferritin [ng/ml] LDH [U/l]	< 1 < 0.5 < 500 9.94-71.70 143-290	13.00 5.87 1981 290.3 308	11.35 1.51 1980 276.2 314	1.24 0.15 1582 218.9 271
Coagulogram	PT [s] INR	9.4-12.5 0.8-1.3	15.0 1.36	12.5 1.13	– –
Proteins	Total protein [g/dl] Albumins [g/dl]	6.2-8.1 3.7-5.6	5.24 2.6	8.14 3.3	9.43 4.2
Cardiac markers	NT-proBNP [pg/ml] T-troponin [pg/ml]		1640 –	216 < 3.00	30 < 3.00
IL-6	IL-6	(< 7.0) [pg/ml]	–	67.49	–
Anti-SARS-CoV-2 antibodies	IgA Index IgM Index IgG [AU/ml]	> 1.1 positive > 1.1 positive > 15 positive	4.52 1.32 90.6		
Urinalysis	Protein [mg/dl] Urine specific gravity [g/ml]	1.015-1.025	103 1.039 Presence of erythrocytes, leukocytes, mucus	Absent 1.017 Presence of mucus	Absent –
Hepatic markers	ASPAT [U/l] ALAT [U/l]	15-40 10-35	– –	51 26	46 31
Calcium	Calcium [mmol/l]	2.19-2.51	In the normal range	2.04	In the normal range
Gasometry	pH pCO_2 [mmHg]	7.35-7.45 35-45	7.31 51.2	Parameters in the normal range	Parameters in the normal range
Cultures (stool. urine and blood)			Negative	Negative	Negative

TABLE 2. Diagnostic criteria of paediatric inflammatory multisystem syndrome associated with COVID-19

Criterium	Recommendation by the Polish Paediatric Society Expert Group	Our patient
Age	Children (0-18 years old)	Eight years old
Fever	Usually > 38.5°C, minimum 3 days	38-40°C longer than 3 days
High inflammatory markers	Elevated CRP, PCT, ESR, fibrinogen, ferritin, LDH, D-dimers	Elevated CRP, PCT, ESR, LDH, ferritin, D-dimers
Multiple organ damage – symptoms from at least 2 organs or systems	• From the digestive system • From the cardiovascular system • From the nervous system • From the respiratory system • Skin and mucosal • Renal symptoms • Features of coagulopathy	• Abdominal pain, tenderness in the mesogastrium • Hypotension, elevated NT-proBNP, decreased EF • Apathy, headache • Features of pneumonia, pleural fluid • Rash (polymorphic), swelling and redness of the conjunctiva, scrotum, hands, and feet, reddening of the auricles, cheilitis with red, cracking, bleeding lips, strawberry or raspberry tongue • Oliguria, signs of acute kidney injury • Prolonged PT and INR
Exclusion of other causes	The differential diagnosis should take into account the following: • infectious and toxic causes, including sepsis, toxic shock syndrome, acute viral disease • acute appendicitis and peritonitis • systemic diseases of connective tissue, proliferative diseases, inflammatory bowel diseases	• Negative cultures and viral antigen tests • Without appendicitis features in abdominal ultrasonography
Relationship with COVID-19 – present at least one of the listed (currently or in the past)	• Positive RT-PCR for SARS-CoV-2 • Positive SARS-CoV-2 antigen test • Positive antibodies to SARS-CoV-2 • Documented significant exposure to COVID-19 in the past 4-8 weeks	• Positive SARS-CoV-2 antigen test • Positive IgG and IgM antibodies to SARS-CoV-2 • 1.5 months earlier quarantine in the boy's class

The patient was discharged from hospital after 11 days in good general condition with the following recommendations:

- acetylsalicylic acid until the control echocardiography and until the further decision of paediatric cardiologist;
- cardiological reassessments after 2-3 months;
- probiotic;
- reduction of physical activity for 2 months;
- influenza vaccination;
- control visit in the clinic after one month, with daily urine collection.

DISCUSSION

The pathogenesis of PIMS-TS is not fully clear, but it seems to be related with immune response dysregulation. Available research indicates a hyperinflammatory state presented by patients with that entity. Elevated levels of cytokines, such as interleukin 18 and interleukin 6 (IL-18 and IL-6), markers of lymphocytic and myeloid activation and peripheral chemotaxis are observed. Patients also present features of activation of natural killer cells, T cells, monocytes, and dendritic cells. Moreover, researchers have shown the presence of autoantibodies against endothelial, gastrointestinal, and immune system cells [2, 3].

The pro-inflammatory status of PIMS-TS patients has common features with other conditions; however, differences in T-cell subsets and the cytokine profile suggest that the hyperinflammation in PIMS-TS can be placed between Kawasaki disease (KD) and acute SARS-CoV-2 infection in adults and children. KD is characterized by higher levels of arteritis and coronary artery disease markers than PIMS-TS, which suggest less severe endothelium involvement in the latter disease. Furthermore, analyses showed that pathogenesis of KD, but not of PIMS-TS, is strongly associated with interleukin 17A (IL-17A), which suggests that IL-17A blocking agents, such as secukinumab, will not be useful in the treatment of this new condition [4].

On the other hand, scientific data elevate the possible role of interleukin 6 (IL-6) in the aetiopathogenesis of PIMS-TS. An elevated level of this substance after interaction with IL-6 receptor leads to enhanced production of other inflammatory cytokines and consequently to initiation of the disease process. The mentioned biological phenomenon resembles the cytokine storm connected with, among others, SARS-CoV-2 infection in adults [5]. This observation suggests that IL-6 or IL-6 receptor are possible targets of severe PIMS-TS treatment, in addition to standard therapy.

However, the treatment of PIMS-TS is not yet conclusively established due to relatively little experience and ongoing research in this field.

TABLE 3. Characteristics differentiating between paediatric inflammatory multisystem syndrome and another example diseases

Kawasaki disease	• Occurs in younger children • Normal concentration of lymphocytes, haemoglobin, platelets, ferritin, BNP, NT-proBNP, troponin I • Less elevated CRP than in PIMS-TS • Absent features of myocarditis, acute left ventricular failure, abdominal pain, diarrhoea, vomiting
Appendicitis	• Pain initially in the epigastric, after a few hours it moves to above right iliac plate (Lanz's point, McBurney's point) • Rovsing's sign, psoas sign, obturator sign • Ultrasound is first-choice examination
Infectious and toxic causes	• Positive bacterial cultures [e.g. *Enterobacteriaceae* ESBL (+), *Mycoplasma pneumoniae*, *Yersinia enterocolitica*] • Positive viral tests (e.g. RSV, influenza, parainfluenza, adenoviruses, enteroviruses and parvoviruses B19) • Positive toxicological tests
Crohn's disease	• Weight loss, avitaminosis, dysphagia, odynophagia, painful mouth ulcers • The disease is chronic with periods of exacerbation and remission • Saccharomyces cerevisiae (ASCA) antibodies are positive • Colonoscopy with the collection of ≥ 2 specimens from the ileum and each segment of the large intestine – visible small ulcers, irregular swelling of the mucosa
Juvenile systemic lupus erythematosus	• Weight loss • Malar ("butterfly") rash, skin rash following sunlight exposure • Discoid rash • Alopecia • Arthritis • Antibody to native DNA or antibody to Sm protein or antiphospholipid antibodies – either anticardiolipin antibodies, presence of the lupus anticoagulant, • Presence of antinuclear antibody by immunofluorescence or an equivalent assay
Still's disease	• Fever occurs every day in the afternoon and evening hours, and responds poorly to antipyretic drugs • Salmon-coloured rash accompanies episodes of temperature increases, usually on the trunk and extremities • Joint pain or arthritis is most severe at the peak of the fever • Laboratory abnormalities are not specified and no indicator is present in this disease pathognomonic
Acute rheumatic fever	• Occurs usually 2-3 weeks after a throat infection with group A *Streptococcus* • Symptoms of cardiovascular system are pancarditis: pericarditis, myocarditis, endocarditis, including valvular inflammation, heart failure • Common symptoms of the other organs are arthritis, involvement of the brain (chorea), and skin (erythema marginatum, subcutaneous nodules)

In accordance with the current state of knowledge, first-line treatment is intravenous infusion of immunoglobulins (IVIG) in total dose 2 g/kg. If the patient presents no improvement after administration, a second infusion of IVIG is not recommended [6]. Intravenous immunoglobulins have multiple functions that modulate and reduce inflammatory reactions. By blocking Fcγ receptors – proteins on the surface of the immune cells – IVIG contributes to impairment of the activation of the innate immune system. IVIG can also block interactions of receptors with target cells, affect lymphocyte differentiation and maturation, and cause cytokine dysfunction [7, 8].

The second-line treatment, applied with IVIG in some conditions or when IVIG is not available or cannot be used, are glucocorticosteroids. Experts suggest starting the therapy with methylprednisolone (2 mg/kg, in 2 doses) and then changing it to oral medication, because CRP will reach the normal range.

Third-line treatment includes biological therapy: IL-1 antagonists (anakinra), IL-6 receptor blockers (tocilizumab), and anti-TNF agents (infliximab) [9]. Thrombocytopaenia is often observed at the end of therapy and requires modification of the ASA treatment. The dose (anti-platelet or anti-inflammatory) depends on the clinical manifestation of the disease.

PIMS-TS should be differentiated with many paediatric conditions, such as Kawasaki disease, rheumatic fever, or appendicitis (more information in Table 3) [10-15].

A characteristic manifestations of PIMS-TS is cardiac dysfunction, including coronary artery dilatation or aneurysms, myocarditis, pericardial effusion, dysfunction of the left ventricle, or even shock. In all children suspected for PIMS-TS, electrocardiogram and echocardiography must be performed. The patients often have elevated levels of troponin and NT-pro-BNP – markers of heart failure, myocardial ischaemia, and damage. Most children with cardiac involvement require paediatric intensive care unit admission and administration of inotropic drugs. The fact that sudden deaths in that group of patients were also documented mean that PIMS-TS should be perceived as a serious and potentially life-threatening condition [10, 11].

Other clinical symptoms include persistent fever, abdominal pain, skin and mucosal involvement, and respiratory or nervous dysfunctions (Table 2).

It is worth underlying that the literature also provides cases of PIMS-TS with haematuria as an early sign of the disease [12] or diarrhoea and fever as the only symptoms presented by the patient [13]. Those cases confirm the need for the conduction of an extended diagnostic process for each child reporting to the hospital, even when the symptoms are not characteristic and specific for PIMS-TS.

Although COVID-19 in children has a rather mild or asymptomatic course, PIMS-TS appearing a few weeks later can lead to serious complications. At 1-2 weeks and 6 weeks after discharge from hospital, clinical reassessments, especially cardiological, are recommended due to the possibility of delayed complications, such as coronary artery aneurysms formation. All patients with PIMS-TS should be excused from physical activity classes for 6 weeks (or until the normalization of coronary arteries imaging abnormalities or troponin level). Other recommendations depends on the clinical condition of the patient and are determined individually.

According to the current state of knowledge, physicians should play a significant role in recommending COVID-19 vaccinations in the paediatric population to prevent infection or severe course of the disease. In Poland, vaccination is available for children who are at least 5 years old (as of 2 January 2022).

DISCLOSURE

The authors declare no conflict of interest.

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