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CASE REPORT

A case of an 11-year-old boy with paediatric inflammatory multisystem syndrome associated with coronavirus disease, haemophagocytic lymphohistiocytosis, and systemic juvenile idiopathic arthritis

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ABSTRACT

After the announcement of the coronavirus disease 2019 (COVID-19) pandemic, a new disease connected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection was described: paediatric multisystem inflammatory syndrome associated with coronavirus disease (PIMS). PIMS is an acute and potentially dangerous inflammatory syndrome that may lead to cardiac complications. It requires differential diagnosis with Kawasaki disease. Some patients with PIMS can develop macrophage activation syndrome (MAS), which until now has occurred most commonly with systemic-onset juvenile idiopathic arthritis (JIA) and is closely related to haemophagocytic lymphohistiocytosis (HLH). In this article we present a case report of a patient with diagnosed PIMS, including PIMS with MAS, and with later diagnosis of HLH and JIA.

KEY WORDS:

paediatric inflammatory multisystem syndrome associated with coronavirus disease, haemophagocytic lymphohistiocytosis, systemic juvenile idiopathic arthritis, COVID-19, macrophage activation syndrome.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) spread throughout the world from the beginning of 2020, and on 11 March 2020 it was recognised as a pandemic by the World Health Organisation (WHO) [1]. A little later, a new disease connected with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection was described: paediatric multisystem inflammatory syndrome associated with coronavirus disease (PIMS) or multisystem inflammatory syndrome in children (MIS-C) [2]. PIMS results from immune dysregulation and is a consequence of a SARS-CoV-2 infection 2–4 weeks earlier (often asymptomatic or minimally symptomatic). PIMS is an acute and potentially dangerous inflammatory syndrome that may lead to cardiac complications [3]; there-

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fore, it requires appropriate medical supervision. Due to similar symptoms to other diseases, differentiation may be difficult. There are many similarities to Kawasaki disease (KD) with an abnormal response of the immune system to a viral, bacterial, or unidentified environmental agent leading to vascular damage and possible cardiac complications [4]. Moreover, very rarely some patients with PIMS can develop macrophage activation syndrome (MAS) [5], which occurs most commonly with systemic-onset juvenile idiopathic arthritis (JIA) and is closely related, and is pathophysiologically very similar, to haemophagocytic lymphohistiocytosis (HLH) [6].

In this article we present a case report of a patient who was twice diagnosed with PIMS, including PIMS with MAS, and who was later diagnosed with HLH and finally with JIA.

CASE REPORT

In September 2021, an 11-year-old boy was transferred to the Department of Paediatrics and Paediatric Endocrinology from a district hospital due to PIMS.

In the history, 8 days before the admission to our department, the patient developed a blotchy rash, first on the thighs, then all over the body (Figure 1). After 2 days, the boy began to be febrile up to 39°C; the next day symptoms such as swelling and pain in the ankle and wrist joints was observed. The primary care physician diagnosed pharyngitis. On the fifth day of fever, due to the lack of improvement, the boy was referred to the hospital. PIMS was diagnosed in the district hospital based on the clinical picture and laboratory tests. The results showed high parameters of inflammation – significantly elevated levels of troponins, aminotransferases, ferritin, and D-dimers (Table 1 0). No RNA of the SARS-CoV-2 virus was detected in a nasal swab using the reverse transcription-polymerase chain reaction (RT-PCR) test. Antibodies against SARS-CoV-2 in the IgG class were reactive, and the rheumatoid factor (RF) concentration was insignificant. The treatment included methylprednisolone (2 mg/kg), immunoglobulin infusion was started, and a third-generation cephalosporin. On the second day of treatment the patient was transferred to our department.

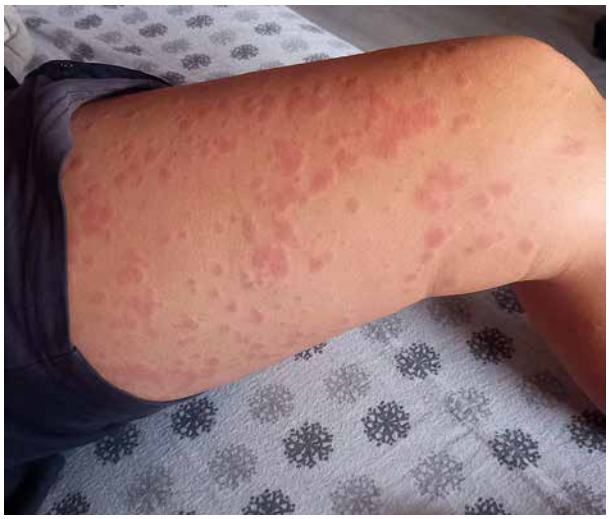

FIGURE 1. A blotchy rash on the thigh

On admission to our department, attention was drawn to a red, blotchy, confluent rash on the skin of the trunk and limbs, reddening of the hands and feet (Figure 2), peeling epidermis in the elbow (Figure 3), knee, and ankle areas, chapped red lips, conjunctival hyperaemia, tongue covered with a white coating, tachycardia (130/min), and hydrocele of the right testicle. The patient reported pruritus. We found out from the medical history that the boy had not been vaccinated against COVID-19. Laboratory tests showed high parameters of inflammation, increased activity of aminotransferases and increased concentrations of γ-glutamyltranspeptidase (GTP), while bilirubin and alkaline phosphatase (AP) concentrations were normal. We found increased levels of lactate dehydrogenase (LDH), ferritin, troponins, and D-dimers as well as disturbances in the lipid profile (Table 1 I). Abdominal ultrasound showed no abnormalities. The consulting cardiologist evaluated normal coronary vessels, and the contractility of the heart was in the lower limit of normal (ejection fraction [EF] = 57–60%). The treatment included methylprednisolone (2 mg/kg/day), transfusion of immunoglobulin, continuation of treatment with use of third-generation cephalosporin, and hepatoprotective drugs as well as acetylsalicylic acid. No bacteria were found in the blood culture. *Escherichia coli* ESBL+ was found in the rectal swab.

In the first 3 days of treatment, the patient was significantly weakened and reported severe pruritus. Then the general condition of the child improved, his fever stopped, and a decrease in the parameters of inflammation was observed.

On the ninth day of hospitalisation, during the reduction of steroid therapy, the patient began to be febrile again, the parameters of inflammation that had already decreased started to increase again, and increased activity of aminotransferases and increased concentrations of GTP were reported, while bilirubin and AP were within the normal range (Table 1 II). Imaging tests were performed – chest X-ray showed no abnormalities, while abdominal USG showed an enlarged liver with enlarged lymph nodes in the hilum. A cardiological consultation was carried out – no changes in the coronary vessels were found, and the contractility of the heart was in the lower limit. Piperacillin with tazobactam and fluconazole were added to the treatment; due to a significant increase in D-dimers nadroparin was added; methylprednisolone pulses were used for 5 consecutive days. A haematological consultation was performed, followed by a bone marrow biopsy. The myelogram showed no features of a bone marrow proliferative disease or haemophagocytosis, and rich cell marrow was described, with a clearly stimulated granulo-

TABLE 1. Results of patient's laboratory tests

Parameters	Standard range	0*	I	II	III	IV	V	VI
WBC [10´3/ul]	4.5–12.5	16.1	17.2	18.54	8.54	15.99	20.19	2.66
RBC [10´6/ul]	3.8–5.8	4.4	4.5	4.42	4.97	4.74	3.91	4.04
HGB [g/dl]	10.8–15.6	12.0	12.2	12.0	12.7	12.9	10.8	10.6
MCV [fl]	69–93	79.8	78.2	79.6	78.1	80.6	79.0	76.7
PLT [10´3/ul]	154–442	285	340	511	358	294	112	102
NEUTR (%)	40–60	92.0	81.5	86.6	57.4	86.1	84.2	50.3
LYMPH (%)	35–55	5.0	7	7.1	30.6	7.6	3.0	45.1
CRP [mg/l]	0–10	254.5	189.8	99.6	8.6	113.2	240	25.4
PCT [ng/ml]	0–0.5	1.16	0.8	0.195	–	–	6.02	0.186
ALT [u/l]	10–45	76	58	191	2231	47	35	106
AST [u/l]	10–40	125	128	146	1692	61	134	455
GTP [u/l]	4–24	–	279	377	163	63.6	150	129
LDH [u/l]	0–342	630	886	477	1017	328	1153	4021
CK [u/l]	0–270	–	102	29	36	25	80	70
CK-MB [u/l]	0–24	–	62	20	29	18	56	54
CREA [mg/l]	0.5–0.99	0.64	0.35	–	0.36	0.48	0.98	0.32
UREA [mg/l]	10.8–38.4	32.23	22.1	–	11.3	13.9	54.9	20.9
CHOL [mg/l]	124–202	–	160	154	120	112	121	209
CHOL-HDL [mg/l]	37–74	–	22	36	32	49	11	63
CHOL-LDL [mg/l]	64–132	–	81.6	93.4	68	45.6	25.6	83.2
TG [mg/l]	22–138	–	282	123	100	422	422	354
FERR [ng/ml]	14–124	19735	17680	8642	3105	1128	> 2000	93950
TROP T [ng/ml]	0–14	1843* $n < 34$	125.9	26.91	3.91	5.89	39.6	7.86
D-DIMERS [ng/ml]	0–500	7055	4193	2774	2589	4841	64386	39956
FIBR [g/l]	2.2–4.2	5.4	5.36	5.36	2.77	5.36	4.34	1.22
IL-6 [ng/ml]	0.0–0.7	–	–	80.1	48.44	212.0	768.3	87.06
NT pro-BNP [ng/ml]	0.0–125	102.3	–	266.8	34.6	173.8	37514.5	319.00
ALB [g/l]	36–56	30.0	30.3	28.9	37.8	37.9	26.8	38.2

ALB – albumin, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CHOL– total cholesterol, CHOL-HDL – high-density lipoprotein cholesterol, CHOL-LDL – low-density lipoprotein cholesterol, CK – creatine kinase, CK-MB – creatine kinase, muscle fraction, CREA – creatinine, CRP – C-reactive protein, FERR – ferritin, FIBR – fibrinogen, GTP – γ-glutamyltranspeptidase, HGB – haemoglobin, IL-6 – interleukin 6, LDH – lactate dehydrogenase, LYMPH – lymphocytes, MCV – mean corpuscular volume, NEUTR – neutrophils, NT pro-BNP – N-terminal prohormone of brain natriuretic peptide, PCT – procalcitonin, PLT – platelets, RBC – red blood cells, TG – triglycerides, TROP T – troponin T, WBC – white blood cells
** hs troponin I*

cyte system, as in autoinflammatory disease, without signs of haemophagocytosis (assessed after steroid therapy). A gastroenterological consultation was also carried out, according to which the diagnosis of hypertransaminasaemia was extended: in the COMBI test we found weakly elevated titre of ANA antibodies (1 : 320) with a fine-grained glow and few nuclear dots, but there was no significant antibody titre in the ANA Profil (ANA examination was after infusion of immunoglobulin). No infection with HAV, HBV, or HCV viruses was found. The first test (qualitative) indicated the presence of Epsteina-Barr virus (EBV) DNA, but the second test (quantitative) did not detect the presence of EBV DNA while the alanine aminotransferase concentration was over 2000 U/l. On this basis, EBV infection was ruled out as a cause of hepatitis.

On the fourth day of administration of pulses with methylprednisolone, the boy's condition improved, his fever stopped, the skin lesions began to subside, he stopped feeling pruritus, and peeling of the epidermis on the fingers was observed. Normalisation of laboratory test results was noticed, but the patient was discharged with persistently elevated levels of C-reactive protein (CRP), GTP, LDH, and ferritin and elevated transaminases. Due to persistent myocardial contractility at the lower limit of normal value, the consulting cardiologist recommended enalapril and a resting lifestyle as well as a check-up in 4 weeks.

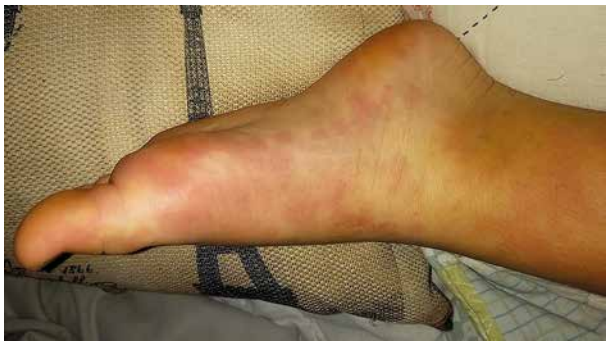

FIGURE 2. A blotchy, confluent rash on the foot

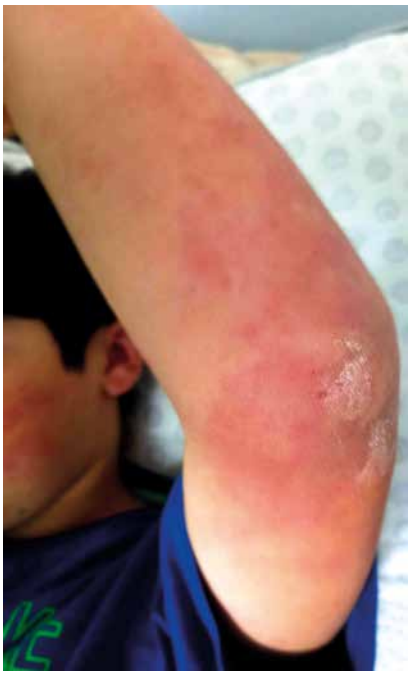

FIGURE 3. A peeling epidermis in the elbow

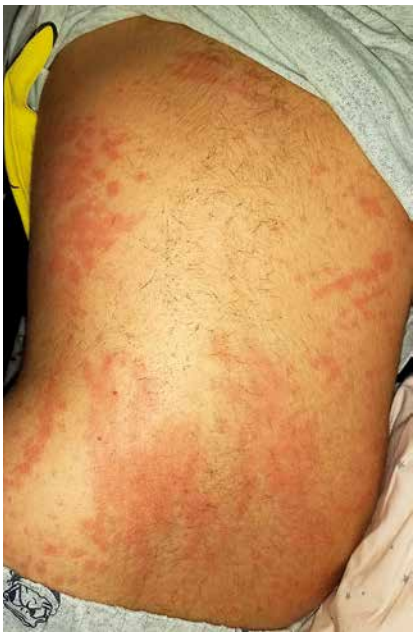

FIGURE 4. A blotchy rash on the trunk

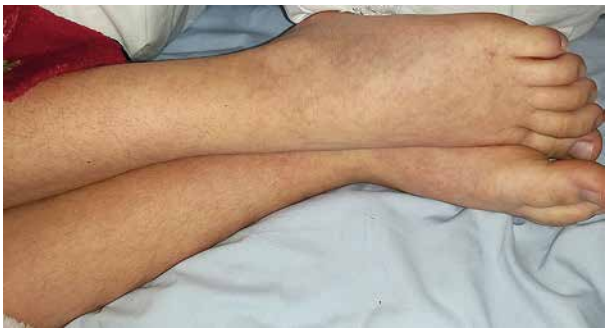

FIGURE 5. A peripheral oedema

After 4 weeks, the boy was admitted to our ward for control tests and arrangement of further management. On admission, attention was drawn to discoloration in places of previous scratches and hydrocele of the right testicle; otherwise, no abnormalities were found. Laboratory tests showed significantly increased activity of aminotransferases and increased concentrations of GTP, LDH, ferritin, and D-dimers (Table 1 III). Cardiologically, the condition was stable. Due to the suspicion of autoimmune hepatitis, the boy was transferred to the Department of Paediatric Gastroenterology. Transferrin isoforms, α-1-antitrypsin, urine and serum copper, and ANCA antibodies were determined. In cholangio-MR, the image of the bile ducts was normal. Liver biopsy showed degenerative hepatocytes, low-grade lymphocytic inflammatory infiltrates, no fibrosis, and normal bile ducts. The unequivocal cause of hypertransaminasaemia was not identified, and the patient remains under the care of a gastroenterologist. During hospitalisation the patient experienced pain in the right testicle. Based on ultrasound image, torsion of the right appendage was suspected and right hydrocele surgery was performed.

Again, the patient was admitted to our department after 2 months due to fever with a rash. Three weeks earlier, due to contact with a person infected with SARS-CoV-2, the boy had RT-PCR test for COVID-19, which turned out to be positive; the patient was asymptomatic. Three weeks after the confirmed infection, the patient became febrile and developed a garland rash all over the body and papular lesions on the hands and feet. The child complained of pain in the wrists and ankles and sore throat. Physically, apart from rash changes, there was a scar after the testicular hydrocele operation, swollen tonsils, and clearly red labial redness. In laboratory tests attention was drawn to increased parameters of inflammation (Table 1 IV). The swab for SARS-CoV-2 was negative (RT-PCR), the presence of reactive antibodies to SARS-CoV-2 in the IgG class was found, but IgM antibodies were non-reactive. Treatment included antibiotics, antipyretics, hydration, and ongoing medications. In next days the patient had a high fever, intensification of skin and mucosal lesions, and peripheral oedema appeared (Figure 4, 5), shortness of breath with saturation drops below 90%, decrease in the alveolar murmur over the lungs

was observed, as well as abdominal pain, loose stools, and oliguria. Deterioration of laboratory test results was noted (Table 1 V). We received information about the absence of bacteria in the blood culture. Growth of *Klebsiella pneumoniae* ESBL+ bacteria in nasal and throat swabs was confirmed. Lymphocyte typification was performed, and the percentage of B and NK lymphocytes was reduced. Abnormalities in laboratory tests were increasing. The chest X-ray showed inflammatory changes, and chest computed tomography (CT) showed confluent densities of the lung parenchyma of a "milky glass" nature and atelectasis-inflammatory changes. On abdominal ultrasound, the liver and spleen were enlarged, with enlarged lymph nodes in the hilum of the liver. The cardiologist found sinus tachycardia, myocardial contractility at the lower limit (EF = 52%), and ventricular septal hypokinesis. The doctor recommended the addition of metoprolol and spironolactone. PIMS was diagnosed, methylprednisolone pulses were administered, immunoglobulins and albumin with a diuretic were transfused, heparin and drugs were administered according to cardiological recommendations, and meropenem was added.

After 4 days of treatment, due to the lack of improvement, an interleukin 1 inhibitor was introduced (2 × 100 mg). In the following days, the patient's general condition improved, his fever subsided, skin lesions and peripheral oedema disappeared, pulse and diuresis normalised, and auscultatory changes over the lungs disappeared. Laboratory parameters also improved with normalisation of morphology parameters and CRP concentration. During whole hospitalisation in our department the boy was never diagnosed with anaemia or hyponatraemia.

During the reduction of the doses of the biological drug and glucocorticosteroid (oral prednisone was used), the boy became feverish again, skin changes appeared – a rash of a variable, polymorphic nature was observed. Increases in inflammation and other biochemical parameters were again revealed (Table 1 VI). Test ANA showed no presence of autoantibodies. The presence of p-ANCA, c-ANCA, and ASCA antibodies was not detected. HIV infection was excluded, as well as HBV and HCV infection. Antibody titres against *Coxsackie B2, B3*, and *B4* viruses were negative. A bone marrow biopsy was performed showing signs of stimulated granulocytic system and phagocytosis. After specialist consultations in the field of haematology, rheumatology, and immunology, it was established the patient did not meet the criteria for HLH, and the clinical picture may suggest MAS in the course of PIMS. The initial dose of anakinra was returned, and methylprednisolone pulses were used. The boy's condition, as well as the results of laboratory tests, improved again. However, during the reduction of steroid and anakinra doses, the boy's condition deteriorated once more, he developed a high fever, and inflammation parameters increased. Steroid therapy was modified (dexamethasone), cyclosporine was added, and improvement was achieved. Due to the features of haemophagocytosis in the myelogram, the boy was transferred to the Paediatric Haematology and Oncology Department.

In the Department of Haematology, after further tests and observation, the diagnosis of HLH without involvement of the central nervous system was confirmed. Haemophagocytosis in the bone marrow was confirmed, the tests showed leukopaenia, anaemia, and thrombocytopaenia; significant hyperferritinaemia and hypofibrinogenaemia were found. Additionally, low level of NK-cells – 2% of lymphocytes, reduced perforin expression in NK-cells – 43.74%, and CD8 lymphocytes – 15.74% as well as high concentration of soluble receptor for IL-2 – 6383 U/ml were found. Treatment was started according to the HLH 2004 protocol (initially dexamethasone and cyclosporine and then etoposide), which was continued for the following weeks. Control chest CT was normal. During the course of treatment the patient had rashes, intertrigo lines, and swellings of the wrist and interphalangeal joints (Figure 6, 7). During the last hospitalisation

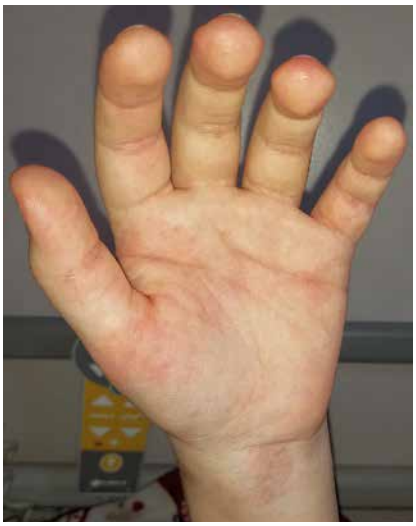

FIGURE 6. Swellings of the wrist and interphalangeal joints

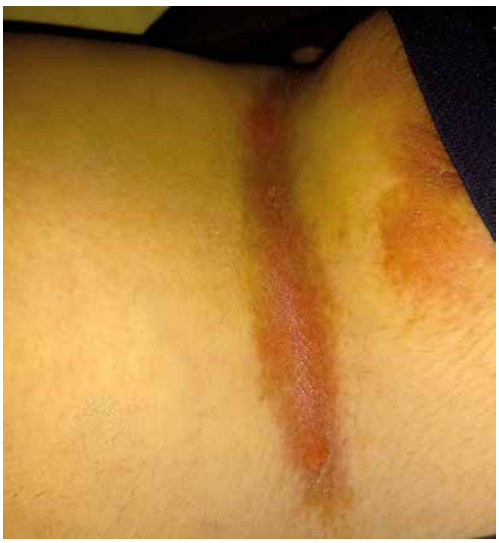

FIGURE 7. Intertrigo lines

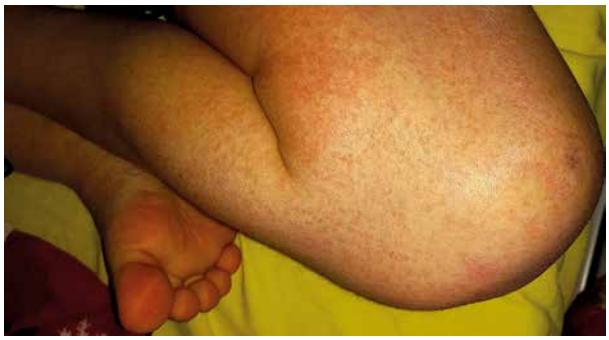

FIGURE 8. An intense, confluent rash

in the Department of Haematology, at the time of discontinuation of glucocorticoids according to the protocol, the child developed a fever, swelling of the ankle joints, and an intense, confluent rash all over the body (Figure 8). Due to the suspicion of systemic juvenile idiopathic arthritis, the boy was transferred to the Department of Paediatric Rheumatology.

On admission to the Rheumatology Department, the boy was diagnosed with bluish-red confluent skin lesions, epidermis peeling on the auricles, inflammation of the corners of the mouth, Cushingoid silhouette, hair loss on the head, and oedema of the left wrist joint. Tuberculosis was excluded, HLA-B27 antigen was negative. No presence of ANA, ANCA, anti-CCP, anticardiolipin antibodies, anti-B-2 glycoprotein antibodies, or RF was found. The diagnosis of JIA was confirmed, and treatment included methylprednisolone, cyclosporine was continued, and then treatment with tocilizumab was started, resulting in the resolution of joint swelling, pruritus, and skin lesions.

Currently, the patient continues treatment with tocilizumab and is under the care of a gastroenterologist, haematologist, and cardiologist. Based on genetic testing, the boy was diagnosed with Gilbert's syndrome. In the last cardiological check-up, myocardial contractility was normal (66%), and the image of the coronary arteries was normal.

The entire medical history is presented in the timeline in Figure 9.

DISCUSSION

The case report shows the severe clinical course of several diagnosed diseases that occurred in our patient. Subsequently, the diagnosis of PIMS was made, then PIMS-MAS, and later HLH and JIA.

There are many similarities between the described diseases, both in clinical symptoms and in their complicated network of relationships and pathomechanisms. In the case of our patient we based our diagnosis of PIMS and MAS associated with PIMS on Polish Paediatric Society guidelines [7]. The diagnosis of haemophagocytic lymphohistiocytosis was based on the 2004 updated HLH criteria, which requires 5 out of 8 of the characteristics [8], and the diagnosis of JIA was based on the International League of Associations for Rheumatology criteria modified in 2001 (Edmonton) [9]. Each of the diseases recognised in our patient are characterised by fever, and in each of them we can observe high concentrations of inflammation parameters, including ferritin. In MAS and HLH, among the common criteria, we also find hypertriglyceridaemia, and in both we can find a reduced number of platelets. It should be noted that also the drugs used in

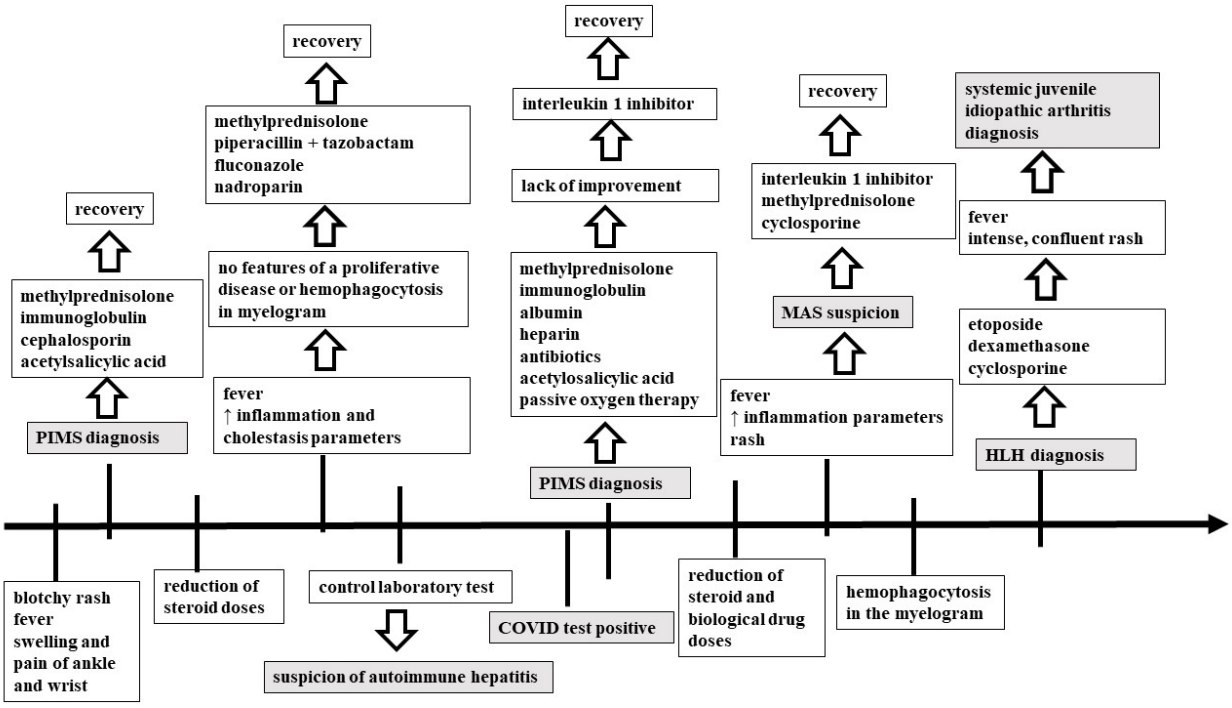

FIGURE 9. Patient symptoms, diagnosis and treatment on timeline

each of the mentioned diseases are partially overlapped. Moreover, in our patient, during both PIMS and HLH, at the time of reducing the doses of glucocorticosteroids, recurrence of symptoms was observed (Figure 9). It can be concluded that although each of the diseases is a separate disease entity, the mentioned disorders are partially associated with similar mechanisms. Additionally, when thinking about each of the mentioned diseases, other causes should always be ruled out, which often leads to difficulties in making clear and unequivocal diagnosis. Moreover, in the diagnosis of MAS, so far associated mainly with JIA, from the moment of the COVID-19 pandemic, causes such as SARS-CoV-2 should also be taken into account as an important triggering factor. For this reason, in the treatment of MAS syndrome in our patient, the recommendations for PIMS management were followed before the diagnosis of JIA was established.

PIMS developed in about 1/1000 children infected with SARS-CoV-2, and its mortality rate was 1.5–2% despite treatment, at the beginning of COVID-19 pandemic [10]. Currently, according to a CDC report from 30 August 2023, PIMS is suppressed [11]. There are several definitions of PIMS in different countries [12, 13]; however, all recommendations take into account the 6 main criteria [7]. Moreover, characteristic constellation of abnormalities in laboratory tests can be helpful in establishing the diagnosis: usually very high rates of inflammation parameters (CRP above 100 mg/l), lymphopaenia, mild anaemia, hypoalbuminaemia, hyponatraemia, and high levels of markers of heart damage: BNP or NT-proBNP, troponin I [3, 10]. In our patient, there was no initial anaemia or hyponatraemia during PIMS recognition.

It is worth to mention that at the beginning PIMS was termed "Kawasaki disease-like", as some patients with PIMS also met the criteria for the diagnosis of KD. Diagnostic criteria for KD were prepared by AHA in 2017 [4].

Very rarely some patients with PIMS can develop MAS. Prior to the COVID-19 pandemic, MAS was mainly diagnosed in children with JIA or systemic lupus erythematosus [6]. Diagnosis of MAS in children with JIA is based on criteria adopted by EULAR, ACR, and the Paediatric Rheumatology International Trials Organisation (PRINTO) [14]. Our patient met MAS recognition criteria as associated with PIMS during the second PIMS diagnosis (Table 1 V).

Haemophagocytic lymphohistiocytosis is a rare, life-threatening immune syndrome characterised by uncontrolled activation of cytotoxic lymphocytes and macrophages. The pathogenesis of secondary HLH remains unclear; however, the most common infectious agent that triggers HLH is EBV [15]. Several features reported in severe COVID-19 and features included in the HLH-2004 diagnostic criteria are common. Therefore, SARS-CoV-2 can be also considered a potential trigger of HLH [16]. Hyperferritinaemia is the most characteristic symptom; also in our patient a significant increase was visible.

CONCLUSIONS

It is important to be aware that all the diseases listed here can lead to serious health consequences, including death. During the diagnosis and treatment of the patient, the work of an interdisciplinary team of specialists is often necessary for proper diagnosis and treatment. We do not have long-term follow-up of many patients after PIMS, so the immunological consequences of these diseases are not fully understood, and a further period of patient observation is needed. It would be reasonable to carry out genetic diagnostics in the direction of immunodeficiency syndromes to provide an answer to the question of why our patient's COVID-19 infection caused such serious consequences.

We hope that the description of our case will show the diagnostic difficulties and serve to develop studies on the pathomechanisms of immune system diseases.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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