CASE REPORT

The Importance of Differential Diagnosis of Pediatric Inflammatory Multisystem Syndrome

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Abstract

Pediatric inflammatory multisystem syndrome (PIMS) is a condition related to the previous exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The pathophysiology of PIMS is not fully understood. However, it can be explained as a consequence of hyperactivation of the immune system. Clinically, PIMS usually follows 2-4 weeks after SARS-CoV-2 infection and its main symptom is fever that lasts for a few days. The diagnosis of PIMS is established by detailed anamnesis, clinical examination, and biological changes such as increasing levels of interleukin-6 (IL-6), D-dimer, NT-proBNP and anti-SARS-CoV-2 IgG antibodies. The intensive treatment should be quickly initiated, as the consequences could be fatal. The treatment is represented by a combination of intravenous immunoglobulins, corticosteroids and anticoagulants.

Keywords: SARS-CoV-2 infection, corticotherapy, immunoglobulins, anticoagulants.

Introduction

Coronavirus disease 2019 (COVID-19) is an air-transmitted illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. It is known that the severity increases with age, usually the population over 65 years old being the most affected. Children and young people have an asymptomatic or mild course of the disease [1,3].

The problem that arises in terms of the pediatric population, in the context of this viral infection, is related to the increasingly severe consequences that require a differential diagnosis as quickly and correctly as possible. These consequences are known as a condition called pediatric inflammatory multisystem syndrome (PIMS) a new disease seen in children directly influenced by previous SARS-CoV-2 infection. The pathophysiology of PIMS is not fully understood. However, it can be explained as a consequence of hyperactivation of the immune system [3-4].

Clinically, PIMS usually follows 2-4 weeks after SARS-CoV-2 infection and its main symptom is fever that lasts for a few days [3-5]. Other manifestations could be represented by rash, fatigue, abdominal pain, red and cracked lips, pharyngeal erythema, swollen hands and feet, peeling skin on hands and feet, headache, conjunctivitis, muscle aches and pains, diarrhea and vomiting, swollen neck glands, unexplained irritability [6-7].

The diagnosis of PIMS is established by corroborating data from anamnesis, clinical examination and paraclinical tests. The

biological changes that can help establishing the diagnosis are: increasing levels of interleukin-6 (IL-6), D-dimer, NT-proBNP and anti-SARS-CoV-2 IgG antibodies [8].

The intensive treatment should be quickly initiated, as the consequences could be fatal. The treatment is represented by a combination of drugs such as intravenous immunoglobulins, corticosteroids, anticoagulants [6].

The treatment of the side effects of corticosteroids should not be forgotten. Treatment with proton pomp inhibitors and a low sodium diet are also important [9].

Case Report

We present the case of a of 1 year and 2 months old child, known with gastroesophageal reflux and recurrent respiratory tract infections, who came to the general pediatric clinic for persistent high fever, chills, altered general status, and impotence of the left lower limb, with the impossibility of supporting orthostatism. The patient was treated with several topic antibiotics at home (azithromycin), but the disease continued to progress. Family history and medical history were unremarkable, except the fact that all his family had been infected with the SARS-CoV-2 virus one month before and he was asymptomatic during that time.

At the clinical examination, the patient had pale skin, a few maculo-papulo-erythematous elements on the face and trunk, a diffuse hyperemic pharynx with microvesicles and impotence of the left lower limb, without inflammatory signs.

Routine blood tests showed mild anemia and thrombocytosis, increased neutrophils with leukocytosis, lymphopenia and increased inflammatory markers (erythrocyte sedimentation rate (ESR) 80mm/h, C-reactive protein (CRP) 60.58mg/dL, fibrinogen 662.221 mg/dL. Also, increased levels of ferritin 258.76ug/L, D-dimers 834.854 ng/mL, Il-6 195pg/mL and NT-proBNP 2175pg/mL were highlighted.

The following tests were performed for guiding the differential diagnosis and turned out negative: procalcitonin and blood cultures for bacterial sepsis, rheumatoid factor for the diagnosis of juvenile idiopathic arthritis (JIA), anti-cytomegalovirus (CMV) and anti-Epstein-Barr (EBV) IgM and IgG antibodies for the diagnosis of these viral infections.

Nasal exudate was also performed, followed by culture, that showed the absence of the beta hemolytic streptococcus group A and the presence of cephalosporin-sensitive MRSA.

Uroculture and coproculture were negative.

Abdominal and pulmonary ultrasounds were normal. The cardiac ultrasound revealed pericarditis with a minimal amount of fluid and a coronaritis that was kept under observation.

PIMS was suspected and for a positive diagnosis anti-SARS-CoV-2 IgG were dosed, and their level was significantly increased (IgG SARS-CoV-2 314.1 AU/mL).

Corroborating the history of the patient, clinical and paraclinical data, the final diagnosis of PIMS was established.

The management of a patient presenting this type of syndrome is challenging. Systemic therapy was initiated, with intravenous antibiotic ceftriaxone 2g/day (7 days), corticosteroids (methylprednisolone 3mg/kg/day initially, then 2mg/kg/day,) immunoglobulins (2g/kg/dose, total dose 19g), aspirin at the recommendation of the cardiologist, antipyretics and gastric protection (intravenous omeprazole).

The treatment was well tolerated and after a week his general condition was highly improved, without fever or other skin or mucosal manifestations; he could also walk without needing any support.

Discussion

The differential diagnosis of PIMS, in this case, includes bacterial sepsis, staphylococcal or streptococcal infection, Kawasaki disease,

juvenile idiopathic arthritis, CMV infection, EBV infection, acute inflammatory demyelinating polyneuropathy (AIDP), the most common form of Guillain-Barré syndrome [10-12].

During the COVID-19 pandemic, children with an inflammatory syndrome resembling Kawasaki disease have been reported [10,11].

The following are components of PIMS that resembles Kawasaki disease in children: persistent fever, inflammation (neutrophilia, elevated CRP level, and lymphopenia), and evidence of single or multiorgan dysfunction, including imaging findings and laboratory study results [10].

Typical or classic Kawasaki disease is characterized by the presence of ≥5 days of fever and ≥ 4 of the following main clinical features: bilateral non-exudative conjunctivitis, erythema of lips and oral mucosa, changes in the extremities, skin rash, and cervical lymphadenopathy [10-11]. The diagnosis of Kawasaki disease is based on the presence of the above clinical criteria: there are neither typical diagnostic features, nor specific diagnostic tests [11-12].

The most fearful Kawasaki disease complications are coronary artery aneurysms, which develop in 15-25% of untreated patients [11].

A prompt recognition of Kawasaki disease is essential, as its prognosis depends on the rapidity of treatment, which is based on intravenous immunoglobulins [11].

Another diagnosis considered was juvenile idiopathic arthritis (JIA), the oligoarticular form. JIA is the most common chronic rheumatologic disease in children, while the etiology is unknown [13].

Several signs and symptoms presented by the child were like those in JIA, such as complaints of joint pain or abnormal joint use, evanescent rash on the trunk and extremities, spiking fevers occurring once or twice each day at about the same time of day [13].

The key to differential diagnosis between PIMS and JIA was the fact that his articular symptoms began four weeks after a SARS-CoV-2 infection, while JIA manifests mostly as a chronic process presenting arthritis for at least 6 weeks before diagnosis (mandatory for diagnosis of JIA) [13].

Acute inflammatory demyelinating polyneuropathy (AIDP) has also to been excluded as diagnosis, due to its severity. The required features for diagnosis are progressive bilateral arms and leg weakness (only legs may initially be involved), absent or decreased tendon reflexes in affected limbs (at some point in clinical course), cranial nerve involvement, especially bilateral facial palsy [12].

No associated hematologic or urinary findings are characteristic of the diagnosis. ESR is normal [12].

In this case, the examination of the cerebrospinal fluid is important for the diagnosis of AIDP but given the lack of signs of meningeal and nerve damage, it was not performed.

The presence of significant inflammatory syndrome and anti-SARS-CoV-2 IgG guided the final diagnosis to a reaction of a previous SARS-CoV-2 asymptomatic infection, also called PIMS.

Conclusions

In conclusion, the diagnosis and management of PIMS are challenging because of differential diagnosis, which must be quick and efficient, especially with Kawasaki disease, as they manifest almost the same.

Also, the follow-up of patients with PIMS is important, because immunosuppressive treatment is needed and complications such as cutaneous effects, electrolyte abnormalities, hypertension, hyperglycemia, pancreatitis, hematologic, immunologic, and neuropsychological effects may appear [9].

Author Contributions:

AM.C. conceived the original draft preparation. AM.C., G.G., VA.I. were responsible for conception and design of the review. AM.C., G.G., and VA.I. were responsible for the data acquisition. AM.C, was responsible

for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. AM.C., G.G., VA.I. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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