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CASE REPORT

Diagnosis and treatment of multisystem inflammatory syndrome temporally related to COVID-19 in an adolescent: case report

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Abstract

In April 2020, the UK pediatric society reported to the World Health Organization the appearance of a rare syndrome, with a wide spectrum of signs and symptoms, temporarily associated with COVID-19, which mainly affected normally healthy schoolchildren and adolescents, with high lethality when not diagnosed and treated early. We present the case of a 12-year-old child who had high and persistent fever, rash and vomiting, who, after 6 days, developed acute respiratory failure, myocardial and renal dysfunction, requiring ventilatory and hemodynamic support, treated with antibiotics, intravenous immunoglobulin, and anticoagulant. The purpose of this report is to present the reader with the peculiar characteristics of the diagnosis and treatment of the syndrome and its main differential diagnoses at the hospital admission.

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INTRODUCTION

In a report sent to the World Health Organization (WHO) in December 2019, the Chinese government described a series of cases of severe pneumonia with high death rates that affected primarily individuals with comorbidities and subjects aged 60 or more years. A taskforce was set up to identify the causative agent of the outbreak. On January 7, 2020, SARS-CoV2, the seventh virus of the coronavirus family identified, was described as the pathogen causing the global health emergency.[1,2]

In mid April 2020, the Royal College of Paediatrics and Child Health reported the appearance of a rare, severe syndrome possibly associated with COVID-19 that affected otherwise healthy school-age children and adolescents. Patients with the condition presented with signs and symptoms and workup findings similar to the ones seen in subjects with Kawasaki disease, macrophage-activation syndrome, and toxic shock syndrome (TSS). Other cases were soon described in Europe, North America, and Latin America. In Brazil, the first cases were described in July.[3,4]

The syndrome comprises a broad spectrum of signs and symptoms involving at least two organs or systems, and may be fatal if patients are left undiagnosed and without early treatment. It stems from the uncontrolled activation of cytotoxic T-cells and massive releases of proinflammatory mediators. About 80% of the patients develop cardiovascular dysfunction, acute respiratory failure, and multi organ dysfunction.[5-7]

The purpose of this article is to provide a description of the peculiarities tied to the diagnosis and treatment of multisystem inflammatory syndrome temporally related to COVID-19 and of the main conditions considered in differential diagnosis at the time of admission. The patient's legal guardian authorized the authors to use data from the medical charts of the patient. The signed informed consent term was submitted to the Research Ethics Committee through Platform Brazil.

CASE REPORT

A previously healthy 12-year-old male adolescent was brought to our service with bouts of holocranial headache of varying intensity occurring for six days in association with fever and photophobia, which stopped for about six hours after the administration of dipyrone. The symptoms appeared one day after he bathed in the waters of a dam near his home. His mother said that he had not presented respiratory symptoms for the past three months. The patient had been taken to a physician twice and was allowed to go home after the administration of intravenous analgesia. Six days after the onset of symptoms he vomited twice and had intense abdominal pain and cramps, with polymorphous exanthems appearing in his torso and arms. His general condition worsened and he had diffuse myalgia, hyporexia, and, according to his medical charts, neck stiffness. The patient was prescribed ceftriaxone 100 mg/kg, two aliquots of crystalloids of 20 ml/kg each, and was referred to the Pediatric Intensive Care Unit (PICU).

The patient was in fair general condition, pale (1+), moderately dehydrated, anicteric, afebrile, and with tachypnea (respiratory rate: 38 breaths per minute) during physical examination at admission. His abdomen was tender to deep palpation, but no signs of abrupt decompression or peritonism were seen. His pupils were equal in size and responsive to light. He had no signs of meningeal irritation and his Glasgow coma score was 15. His extremities were well perfused and his pulses were full and symmetrical; capillary refill time was three seconds.

Laboratory (Table 1) and imaging tests (Table 2) were performed. The patient was monitored and offered oxygen with a nasal cannula. Doxycycline was added to his prescription of ceftriaxone and he was placed on isolation until his test results were available. Differential diagnosis included abdominal sepsis, dengue, and leptospirosis.

Tachypnea worsened 12 hours after admission to the PICU and the patient developed subcostal retractions. His extremities were cold; his pulse was weak; capillary refill time increased (4-5 seconds); urine output decreased; and blood pressure (BP) levels decreased (systolic BP 85 mmHg; diastolic BP 40 mmHg; mean BP 55 mmHg). The patient was promptly intubated and was infused crystalloids twice for volume expansion. A central line in the right internal jugular vein was used to infuse adrenalin at a rate of 0.3 mcg/kg/minute. Vesicular breath sounds were not heard in the base of the lungs; chest computed tomography scans and X-ray images showed signs of bilateral pleural effusion. The patient was immediately submitted to a chest drainage procedure.

With these complications in mind, the care team decided to replace ceftriaxone with piperacillin/tazobactam associated with clindamycin. Toxic shock syndrome was considered in differential diagnosis, and macrophage-activation syndrome was not ruled out.

On the second day at the PICU, the patient was prescribed norepinephrine for hemodynamic support followed by hydrocortisone. Furosemide was added to improve urine output and help manage acute kidney injury.

Three days after the patient was admitted to the PICU (9th day of symptoms), the team had access to his serology and RT-PCR tests for SARS-CoV-2; two samples sent for IgG testing were positive, while the RT-PCR test was negative. The choice was made to prescribe intravenous immunoglobulin 2 g/kg, enoxaparin 2 mg/kg/day, and replace hydrocortisone with methylprednisolone. A transthoracic echocardiogram showed an ejection fraction of 54%, good heart contractility, and no coronary involvement.

Three days after the administration of immunoglobulin (6th day at the PICU and 12th day of symptoms), the patient became afebrile. Support therapy with vasoactive drugs was stopped and the patient was extubated eight days after admission to the PICU. The patient was discharged twelve days after admission.

Table 1. Laboratory tests performed upon Intensive Care Unit (ICU) admission.

Complete Blood Count
• Hemoglobin: 10 g/dl
• Hematocrit: 28%
• White Blood Cells: 15,800 /mm³
(Rods: 6%; Segmented: 62%)
• Platelets: 50.000/mm³
Sodium: 138 mmol/L
Potassium: 4.4 mmol/L
Calcium: 8.0 mmol/L
Magnesium: 1.3 mmol/L
Glucose: 80 mg/dL
Bilirubin: 3.1 mg/dL (Direct: 2.4 mg/dL)
GOT: 68 U/L
GPT: 53 U/L
Ferritin: 476 µg/L
ESR: 93 mm
CRP: 43 mg/L
Triglycerides: 215 mg/dL
BUN: 82 mg/dL
Creatinine: 1.0 mg/dL
APTT: 64
PT: 1.44
Fibrinogen: 211 g/L
Troponin: 128 ng/mL
CSF
• Red Blood Cells: 1
• White Blood Cells: 4 (differential count was not possible)
Cultures
• Blood Culture 2 samples (central and peripheral): Negative
• Urine Culture: Negative
• CSF Culture: Negative
COVID-19 / SARS-CoV 2
• IgM: Negative IgG: Positive (test was confirmed and repeated)
• RT-PCR: Negative

Table 2. Imaging Tests.

• Chest CT scans: bilateral pleural effusion. No lung parenchyma involvement.
• Abdominal US: small quantities of free fluid in the abdominal cavity. Gull bladder with increased wall thickness suggestive of inflammation.
• Chest X-ray images: signs suggestive of bilateral pleural effusion.
• Echocardiogram: good segmental contractility, ejection fraction of 54%, no valve involvement or alterations in major base vessels. Coronary arteries unaltered.

DISCUSSION

The signs and symptoms of COVID-19 are similar to the ones described in the majority of respiratory viral infections typically seen during childhood. Severe cases are rare, and most occur in children aged less than one year, with a history of preterm birth, and individuals with comorbidities (heart disease, diabetes, liver disease, and inborn errors of metabolism). Multisystem inflammatory syndrome in children (MIS-C) usually affects school-age children and adolescents; the disease causes significant alterations in inflammatory and cardiac markers, as seen in this case report.[8,9]

The diagnosis of MIS-C related to COVID-19 is defined based on the criteria established by the WHO (Table 3). In addition to signs, symptoms, and laboratory evidence of MIS-C, diagnosis is based on the confirmation of infection by SARS-CoV-2, seroconversion or exposure to individuals with COVID-19 in the four weeks preceding the onset of symptoms.[10]

Inflammatory syndrome or cytokine storm causes immune alterations that trigger a broad spectrum of signs and symptoms (high persistent fever, exanthems, vomiting, myocardial and kidney dysfunction) and is an element in the diagnostic criteria for MIS-C, although it may be present in other conditions such as Kawasaki disease shock syndrome and toxic shock syndrome, particularly in female adolescents.[11]

Patients with MIS-C progress rapidly to severe disease, which includes lung, cardiovascular, hematological, and kidney involvement. Patients require referral to an intensive care unit or monitoring at an emergency room. Diagnosis is rarely performed at admission, since serology, RT-PCR, and other laboratory and imaging tests are needed. Thus, patients are initially offered supportive care to maintain airway patency, oxygen therapy to keep good oxygen arterial pressure and saturation levels, hemodynamic support, measures to provide for proper fluid and electrolyte balance and water supply to maintain good urine output levels.[12]

Patients with sepsis with or without signs of shock must be promptly prescribed empirical antibiotic therapy considering signs and symptoms and local epidemiology. Since in the case in question toxic shock syndrome was one of the conditions considered in differential diagnosis, the patient was prescribed clindamycin, a semisynthetic antibiotic agent obtained by 7(s)-chloro-substitution of the 7(R)-hydroxyl group of lincomycin, which binds to the 50S sub-unit of bacterial chromosomes and prevents peptide bond formation, thereby inhibiting the growth, reproduction, and release of TSS-inducing toxins.[11,13]

Immunoglobulin must be considered in cases of moderate to severe MIS-C and in cases meeting the criteria for complete or incomplete Kawasaki disease. In individuals with TSS, it may neutralize bacterial superantigens and modulate immune response. The indicated dose is 1 to 2 mg/kg, infused for 12 hours and administered a second time in cases of refractory disease.[12,14]

Methylprednisolone is the steroid of choice in severe cases when associated with immunoglobulin (pulse therapy or in the usual dose of 1 to 2 mg/kg every 6 hours) or in refractory cases. Immunomodulators should only be prescribed in cases refractory to immunoglobulin and steroid pulse therapy. There is no evidence supporting the use of antivirals.[14]

As the pandemic advances, many studies have reported increases in the incidence of thromboembolic events in patients

Table 3. Criteria for the definition of MIS-C.

• High persistent fever (> 39° for more than 3 days);
AND
• At least two of the following signs and/or symptoms:
- Non-purulent conjunctivitis;
- Bilateral rash;
- Mucocutaneous inflammation signs (oral, hands or feet)
- Hypotension or shock
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities*
- Coagulopath
- Acute gastrointestinal problems
AND
• Elevated markers of inflammation (CRP, ESR, or procalcitonin)
AND
• Rule out other conditions in differential diagnosis
AND
• Evidence of SARS-CoV-2 infection, seroconversion, or exposure to patients with COVID-19 in the four weeks preceding the onset of symptoms

MIS-C: multisystem inflammatory syndrome in children. (Adapted from WHO, 2020)[10]

* Includes echocardiogram findings, increased troponin and proBNP

with severe forms of the disease. Although our patient did not meet the criteria for Kawasaki disease and did not have evidence of coronary aneurysms or an ejection fraction < 35% in his echocardiograms, we opted to keep him on enoxaparin on account of the state of hypercoagulability he was in.[15]

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