Multi-system inflammatory syndrome in children and macrophage activation syndrome: case study

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ABSTRACT

The Multi-System Inflammatory Syndrome in Children (MIS-C) is a condition characterized by hyperinflammatory phenomena, complicating SARS-Cov 2 infections in the pediatric population. It may occasionally trigger macrophage activation syndrome (MAS) and could lead to multiorgan system dysfunction. We report the observation of three patients who were hospitalized in the department of pediatrics, emergency and resuscitation of the University teaching hospital Hedi Chaker of Sfax during the year 2021. All of them had marked clinical and biological signs of inflammation confirming the MIS-C, but also strongly evoking SAM. The study of bone marrow showed the intra medullary hemophagocytosis. Prompt diagnosis and suppression of systemic inflammation using Venoglobulin, methylprednisolone and aspirin were associated with a favorable outcome. Heparin therapy was indicated for D-dimer levels above 3000, and dobutamine was combined when left ventricle function was affected. Stabilization of general condition and apyrexia were obtained for the three children within 48 hours. Further studies to investigate the long-term outcome of these patients are proposed.
Keywords: COVID-19; Multi-System Inflammatory Syndrome in Children; Macrophage activation syndrome

RÉSUMÉ

Le syndrome inflammatoire multisystémique chez l'enfant (MIS-C) est une affection caractérisée par des phénomènes hyperinflammatoires qui compliquent les infections par le SRAS-Cov 2 dans la population pédiatrique. Il peut parfois déclencher un syndrome d'activation des macrophages (SAM) et conduire à un dysfonctionnement de plusieurs organes. Nous rapportons l'observation de trois patients qui ont été hospitalisés dans le département de pédiatrie, d'urgence et de réanimation de l'hôpital universitaire Hedi Chaker de Sfax au cours de l'année 2021.Tous présentaient des signes cliniques et biologiques marqués d'inflammation confirmant le MIS-C, mais évoquant aussi fortement le SAM. L'étude de la moelle osseuse a mis en évidence l'hémophagocytose intramédullaire. Un diagnostic rapide et la suppression de l'inflammation systémique par la veinoglobuline, la méthylprednisolone et l'aspirine ont été associés à une issue favorable. Le traitement par héparine était indiqué pour des taux de D-dimères supérieurs à 3000, et la dobutamine était combinée lorsque la fonction ventriculaire gauche était affectée. Une stabilisation de l'état général et une apyrexie ont été obtenues pour les trois enfants dans les 48 heures. D'autres études sont proposées pour étudier les résultats à long terme de ces patients.
Mots clés : COVID-19 ; Syndrome d'inflammatoire multisystémique de l'enfant ; syndrome d'activation macrophagique

INTRODUCTION

Covid-19 infection was considered to be child-sparing on previous reports, although it remains unclear if this is due to a lack of detection because of predominantly asymptomatic or mild disease in this age group. However, the appearance of this virus was followed by an emergence of a number of cases of children presenting with inflammatory shock that was secondarily attributed to coronavirus (1). The Multi-System Inflammatory Syndrome in Children (MIS-C) following coronavirus infection includes fever, severe illness, and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of covid19 infection (2,3). The MIS-C may occasionally trigger macrophage activation syndrome (MAS) and could lead to multiorgan system dysfunction (4). We present these cases to increase familiarity among pediatricians with the clinical manifestations of this association.

METHODS

We report the observation of cases that were hospitalized for management of MIS-C and MAS associa-

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tion. This study was conducted in the department of pediatrics, emergency and resuscitation of the University teaching hospital Hedi Chaker of Sfax during the year 2021.To define MIS-C, we based on the case definitions established by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (2,3). To define MAS, we based on the HLH-2004 criteria (5).

RESULTS

The first child, L.S. was 6 years old, with no previous history of illness. She came with a fever of up to 40°C, abdominal pain and vomiting for 5 days. The grandmother was infected with coronavirus 3 weeks ago. On examination, the child was asthenic. She had bilateral conjunctivitis. Signs of heart failure as hepatomegaly, hepato-jugular reflux and hypotension were present. In biology, she had leuko-lymphopenia at 650/mm3 and thrombocytopenia at 99 000/mm3. Inflammatory markers, C-reactive protein (CRP) and ferritinemia, were high, 199 mg/L and 5649 ng/mL respectively. Fibrinogen was normal at 2,6g/L. Ionogram showed hyponatremia at 128 mmol/L. Triglyceride were elevated at 3.9g/L. The markers of the different organs showed a multivisceral damage: troponin, D-dimer and transaminase levels were high: troponin at 185.8ng/L; AST/ALT at 58/69 UI/L and D-dimer at 5649µg/L. She underwent an ultrasound to assess cardiac function, which was low at 40%. The diagnosis of MISC was supported by a positive covid serology and a negative PCR, indicating previous involvement. However, due to the strong suspicion of an associated macrophage activation syndrome, the child had a sternal puncture confirming the intra medullary hemophagocytosis. The second child, B.A, was a 6 year-old girl presented to our emergency department with fever and generalized skin rash. She had been healthy until 4 days prior to arrival, at which point she developed elevated temperature (39°C - 40°C) and asthenia. Upper or lower respiratory tract symptoms were absent. Vital signs at the time of examination showed heart rate of 150 beats/min, blood pressure of 70/30 mm Hg, respiratory rate of 20 breaths/min, and an oxygen saturation of 99% on room air. Physical examination revealed a generalized skin rash extending over the upper limbs, lower limbs and trunk, clearing with vitro pressure. She also had conjunctivitis and cheilitis. A chest x-ray did not have any evidence of infiltrates or cardiomegaly. Laboratory analysis was remarkable for leukolymphopenia at 560/mm3 and thrombocytopenia at 42000/mm3. She also had a slight transaminitis with AST 90 UI/L and ALT 101 UI/L. Her D-dimer and CRP were both significantly elevated at 8000 µg/L and 163 mg/L, respectively. Ferritinemia was high at 1409 ng/mL. While troponin and fibrinogen were at normal rate. Cardiac ultrasound showed a moderate dilatation of the right coronary with correct left ventricular ejection function (LVEF) 60%. Although contacts with any known sick person were denied, PCR covid was weakly positive and covid serology was positive. Clinical suspicion of macrophage activation syndrome associated with the MISC syndrome led to sternal puncture that confirmed the diagnosis.

The third patient, R.B, was a previously healthy 6-year-old female child, admitted with a history of measured fever for 4 days, with an altered general condition and asthenia. Concomitantly, she presented gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain. On admission, the patient was confused and agitated. She was in respiratory distress. She had superficial polypnea, marked signs of struggle and an oxygen saturation of 60% on room air indicating severe hypoxia. Other vital signs at the time of examination revealed heart rate of 120 beats/min and blood pressure of 90/63 mm Hg. She had a generalized maculo-papular rash with breech erythema and bloated abdomen with hepatomegaly. Initially, chest x-ray showed acute pulmonary edema. This was prior to the echocardiography that showed biventricular dysfunction, LVEF at 30% with global hypokinesia, dilated right chamber, dilated pulmonary artery and pulmonary arterial hypertension. The pericardium was dry. Laboratory tests showed leukon lymphopenia at 640/mm3 with anemia at 6.3g/dL and thrombocytopenia at 117000/mm3. Her D-dimer and troponin were both significantly elevated at 4400 µg/L and 121 ng/L, respectively. She also had a significantly high CRP 205 mg/L and ferritinemia 321ng/mL, and slightly high fibrinogen at 4.05 g/L. Contact with sick persons was confirmed. Actually, her mother had the flu 3 weeks ago. PCR covid was negative while Covid serology was positive. The myelogram confirmed the macrophage activation syndrome. Treatment was promptly initiated for all three patients. They were treated with Venoglobulin 2g/kg, methylprednisolone 10mg/kg/d, aspirin 5 mg/kg/d and heparin therapy for D-dimer levels above 3000. Dobutamine was combined with treatment for the first and third cases due to an affected LVF. Stabilization of general condition and apyrexial were obtained for the three children within 48 hours.

DISCUSSION

Pediatric Covid-19 infection is mild, and almost all children recover entirely. Yet, it can be complicated by a late but marked immunogenic response and trigger MIS-C, presenting with fever, hypotension, severe abdominal pain and cardiac dysfunction (6). In our serial, the diagnosis of MIS-C was confirmed using the case definitions established by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (2,3). It is a dangerous hyperinflammatory condition which can subsequently lead to MAS: uncontrolled activation and proliferation of macrophages leading to end-organ dysfunction with high morbidity and mortality (4,7). The diagnosis of MAS is based on association of clinical and biological elements. Based on the HLH-2004 criteria (table1), and independently of any particular context, the diagnosis of SAM is fulfilled by meeting five out of the eight criteria below There are no specific criteria to diagnose MAS in the MIS-C, yet, the diagnostic criteria for MAS in the setting of juvenile idiopathic arthritis have been applied by Verdoni and Al (8) in the setting of kawasaki disease.

Table 1: Diagnostic criteria for macrophage activation syndrome according to HLH-2004 criteria (5)

1. Fever
2. Splenomegaly
3. Cytopenias affecting two out of three blood lineages in peripheral blood Hemoglobin < 9 g/dL [in infants < 4 weeks: hemoglobin < 10 g/dL) Platelets < 100 000 /ml Neutrophils < 1000 /ml
4. Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥ 3.0 mmol/L [2,65 g/l) Fibrinogen ≤1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes, and no malignancy
6. Low or absent natural killer cell activity
7. Ferritin ≥ 500 mg/L
8. Soluble CD25 ≥ 2400 U/mL

Hence, they are not specific to Kawasaki, but given the clinical similarity between MIS-C syndrome and Kawasaki disease, we may suggest applying them when HLH-criteria are not achievable.

The criteria to diagnose MAS in the setting of juvenile idiopathic arthritis are as detailed in table 2. To receive the diagnosis, all criteria must be met (5).

Table 2: The criteria to diagnose macrophage activation syndrome in the setting of juvenile idiopathic arthritis (5)

1. Fever
2. Ferritin greater than 684 ng/mL
3. Platelet count less than 181 000/ml
4. Aspartate transaminase [AST) greater than 48 U/L
5. Triglycerides greater than 1,56 g/l
6. Fibrinogen less than 3,6 g/l.

Our patients fulfilled both the classical criteria and partially the criteria in the setting of juvenile idiopathic arthritis, and the diagnosis of MAS was confirmed with no doubt.

Initial studies at the beginning of the coronavirus epidemic suggested that MAS was a complication of the immune response during the infectious episode of coronavirus. This theory is supported by the fact that MAS can be secondary to any acute infectious episode. Subsequently, it was described as a differential diagnosis of MIS-C syndrome (9).

In fact, some features of MIS-C showed similarities to MAS and responded to its treatment protocols. However, some research suggests distinct clinical and laboratory differences between MIS-C and MAS. Like ESR [erythrocyte sedimentation rate) which is classically low in MAS, but remarkably high in MIS-C. Also, splenomegaly is a hallmark of MAS, but is not seen in MIS-C (6). The clinical and laboratory features of MIS-C relate to known syndromes of hyperinflammation and cytokine storm in children, including MAS, are under study. Lee and Al (7) found that MIS-C shares some features with inflammatory processes in MAS, but also possesses distinct characteristics. In fact, the laboratory findings in MIS-C are suggestive of a MAS-like cytokine storm. However, differences in the degree of elevation of markers like ferritin, IL-18, and CXCL9 suggest that the pathogenic cytokines driving MIS-C likely diverge from those driving MAS. Then recently, the immunological spectrum of MIS-C and its relationship with other inflammatory conditions were studied: MIS-C and MAS have been shown to be associated (6). In the study of Lima-Setta and Al (10) including 56 patients with MIS-C, MAS was associated with MIS-C and described to be a potential harmful complication of this hyperinflammatory condition in up to 2% of children. These different theories result from the fact that the case definitions of MIS-C established by the CDC and the WHO are extremely wide and complicate the identification of its true spectrum and potential complications. It would be found in many children with acute viral infection such as coronavirus, systemic onset juvenile idiopathic arthritis, and many other infectious and inflammatory conditions of childhood like MAS (6). On the other hand, acquiring secondary MAS in children can complicate many pathologies: infections, neoplasia, systemic inflammatory or autoimmune diseases. We can conclude that all these theories are likely to be possible. MAS is a critical situation that threatens the patient's vital prognosis. If not treated in time, it can be lethal. Hence the importance of early identification and prompt initiation of appropriate therapies (4). In addition, cases of death during MIS-C have been described in the absence of treatment. Prompt diagnosis and suppression of systemic inflammation are associated with a favorable outcome in most cases (7). In our study, despite this potentially fatal association, we noted a good outcome for all patients. Luck fully, both MIS-C and MAS treatments are based on anti-inflammatory and immunosuppressive agents, thus improving the prognosis of their association (4,7).

CONCLUSION

MIS-C is a life-threatening condition, which complicates the evolution of a coronavirus infection in some children. We are still learning from worldwide collaborative studies about this disease, their relationship with other inflammatory conditions and their eventual complications. In this study, we reported the association with MAS, a secondary dangerous complication induced by the important inflammatory phenomena and by the important cytokine storm. The immunological mechanisms and pathophysiological phenome-

na leading to this combination of two life-threatening conditions are not yet clear. Thankfully to date, the treatment administered for MIS-C has contributed to the successful outcome of MAS as well. Nevertheless, several studies are underway to elucidate these phenomena in order to administer improved treatment and further improve the prognosis of patients. Given the novelty of MIS-C, we do not have enough insight into the later outcome of these patients, especially in the case of complications with MAS. We may propose to do further studies to investigate the long-term outcome of these patients compared with those who had an episode of MIS-C without complications.

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