

Macrophage activation syndrome: a rare complication of multisystem inflammatory syndrome in children related to COVID19

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ABSTRACT :

Macrophagic activation syndrome (MAS) also known as secondary hemophagocytic lymphohistiocytosis, is a rare and potentially fatal condition that has been described as a rare complication of multisystem inflammatory syndrome in children (MIS-C) related to COVID19. Here we report a 9-year-old-girl who presented MAS complicating MIS-C.

Key words : macrophagic activation syndrome, multisystem inflammatory syndrome in children, child, Kawasaki disease, COVID19

INTRODUCTION :

COVID-19 multisystem inflammatory syndrome in children (MIS-C) is a potentially life-threatening condition characterized by immune dysfunction with multisystem involvement; that can occur 3 to 6 weeks after primary SARS-COV2 infection [1]. Macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis, has been described in adults with severe acute COVID 19 infection [2], in children with Kawasaki disease (KD) which is a vasculitis that clinically overlaps MIS-C [3] and in children with MIS-C [1]. Herein, authors report a case of MIS-C complicated with MAS.

CASE REPORT :

A 9-year-old girl presented with one week history of fever accompanied by abdominal pain and vomiting. A family COVID 19 exposure was reported one month ago. On physical examination, temperature was 39°, she had tachycardia (125 beat/mn), blood pressure 90/50 mmHg, diffuse abdominal tenderness and infracentimetric cervical lymphadenopathy. A complete blood count and laboratory tests revealed pancytopenia (white blood cells: 4920/mm³, neutrophils: 980/ μ L, Hb, 9g/dL, platelets: 98000/mm³), C-reactive protein, 70mg/l, erythrocytation rate (ESR), 116 mm, aspartate aminotransferase (AST), 395 UI/l, alanineaminotransferase (ALT), 241 UI/l, natremia, 125 mmol/l, lactate dehydrogenase (LDH) elevated to 1358 u/l, ferritinemia increased to 2849 ng/ml, and triglycerides, 3 mmol/l. renal function was normal. Abdominal ultrasound showed homogeneous hepatosplenomegaly. Chest X-ray was normal. Blood culture and cytobacteriological exams were negative. Serologies for hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus, Parvovirus B19 and HIV were negative. In view of the suspicion of MIS-C, we completed with RT PCR SARS COV2 which was negative, however, SARS-CoV-2 serology was positive with presence of Ig M and IgG. D-Dimers were elevated 4911 ng/ml. The echocardiogram was normal. We also suspected MAS; bone marrow aspiration was performed showing the presence of numerous images of hemophagocytosis (Fig 1).

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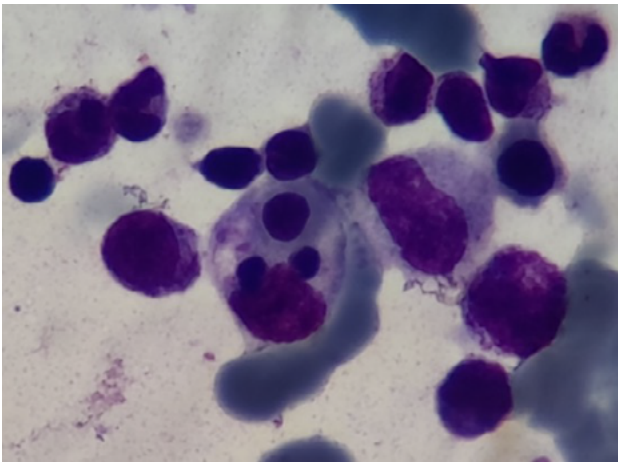


Figure 1 : Bone marrow aspiration showing macrophage (arrow) phagocytosing erythroblasts.

Treatment was started with intravenous immunoglobulins (IGIV) (2g/kg/day), acetylsalicylic acid (3mg/kg/day) and intravenous methylprednisolone (2mg/kg) with resolution of fever. Digestive symptoms disappeared after 4 days. All biological disorders totally disappeared after one month. The follow up was 5 months.

DISCUSSION :

Authors describe a rare association of MIS-C and MAS in a previously healthy child. To the best of our knowledge, this association was described in the literature in three studies. In a prospective study [1], published in 2021, eight of 19 (42%) patients with MIS-C fully satisfied 2016 MAS criteria [4]. In two previous studies published in 2020, MAS was reported in 30 (25%) among 118 children included in these studies [5,6].

Our patient fulfilled WHO criteria of MIS-C [7]. In fact, she presented fever for more than 3 days, abdominal pain, elevated inflammatory markers, elevated D Dimer and SARS COV 2 exposure with positive serology; she also satisfied 2016 MAS criteria (prolonged fever, hepatosplenomegaly in the abdominal ultrasound, high ferritin level, pancytopenia and hemophagocytic images in bone marrow aspiration).

Multisystem inflammatory syndrome in children related to SARS Cov2 was initially described in the UK in April 2020 [8], it's a severe post-infectious complication that can occur 3 to 6 weeks after a typically mild or asymptomatic SARCOV2 infection [1]. It was initially described as Kawasaki like disease or pediatric inflammatory multisystem syndrome temporally associated with SARS-Cov2 (PIMS-TS) and became known as MIS-C in the USA. Our patient probably contracted SARS-COV2 infection one month ago and was asymptomatic.

MIS-C has been characterized as the presentation of a child with high, persistent fever with elevated inflammatory markers (C reactive protein and ESR) and evidence of single or multiorgan system dysfunction [2] especially cardiac dysfunction. Biological findings can include lymphopenia, high D dimer

levels, high ferritin levels, high LDH, high transaminase levels and elevated cardiac biomarkers.

The characteristic of this syndrome resembles those of Kawasaki disease which is a vasculitis that can lead to coronary artery abnormalities (persistent fever, exanthema, chelitis, conjunctivitis, cervical lymphadenopathy, changes in the extremities and cardiac involvement). KD complicated with MAS had been reported in a systematic review, which identified 67 child with KD and MAS [3]

There is also a significant overlap between features reported in MIS-C and those included in MAS diagnostic criteria (persistent high fever, high serum ferritin levels, elevated liver enzymes, cytopenia); some authors considered that MIS-C is consistent with KD with subsequent MAS [9].

The pathophysiology of MAS in MIS-C remains poorly understood. A review has suggested that the hyperinflammatory syndrome associated with COVID19 may have a significant pathogenic overlap with viral induced HLH (macrophagic activation, release of high levels of circulating cytokines and impairment of NK cells and CD8+ cells) [10]

The mainstay of treatment of MAS with MIS-C is the same which was recommended for MIS-C; it consists on administration of IGIV, antiplatelet therapy and steroids.

CONCLUSION :

The recently described hyperinflammatory syndrome related with COVID 19 can be associated with MAS. In the presence of cytopenia, and other MAS criteria, macrophage activation syndrome must be considered in children with MIS-C and, a prompt treatment must be initiated. Delaying treatment may impact clinical outcome in children with MAS complicating MIS-C.

CONFLICT OF INTEREST :

Authors declare no conflict of interest

ABBREVIATIONS :

COVID 19: coronavirus disease 2019

HLH: Hemophagocytic lymphohistiosis

HIV: Human immunodeficiency disease

KD: Kawasaki Disease

LDH: lactate deshydrogenase

MIS-C: multisystem inflammatory syndrome in children

MAS : macrophage activation syndrome

NK : Natural Killer

PIMS-TS: Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-Cov2

SARS Cov2: severe acute respiratory syndrome coronavirus

IGIV: intravenous immunoglobulin

RT PCR: Real Time Polymerase Chain Reaction

WHO: World Health Organization

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