Title: Macrophage Activation Syndrome in a child with Juvenile Idiopathic Arthritis secondary to SARS-CoV-2

Short title: MAS in JIA triggered by SARS-CoV-2

Hacer Akturk, MD, Department of Pediatrics, Pediatric Infectious Disease Unit, Koc University Hospital, Istanbul, Turkey

Murat Tanyildiz, MD, Department of Pediatrics, Pediatric Intensive Care Unit, Koc University Hospital, Istanbul, Turkey

Fatih Erbey, MD, Department of Pediatrics, Pediatric Hematology&Oncology Unit, Koc University Hospital, Istanbul, Turkey

Mehmet Tasdemir, MD, Department of Pediatrics, Pediatric Nephrology Unit, Koc University Hospital, Istanbul, Turkey

Aydın Celikyurt, MD, Department of Pediatrics, Koc University Hospital, Istanbul, Turkey

Emel Gonen, MD, Department of Orthopedics, Koc University Hospital, Istanbul, Turkey

Ilmay Bilge, MD, Department of Pediatrics, Pediatric Rheumotology Unit, Koc University Hospital, Istanbul, Turkey.

Corresponding Author

Hacer Akturk,

Postal adress: Koc University Hospital, Department of Pediatrics, Davutpaşa Caddesi No:4, 34010, Topkapi, Istanbul, Turkey,

E-mail: hacergunakturk@gmail.com; Phone: +90850 250 8 250.

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Summary:

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a pandemic affecting many countries and millions of people. Physicians has encountered some rare and challenging cases related to SARS-CoV-2, a novel virus with still many unknowns. In order to share our experience of a such clinical picture, we present here a child with SARS-CoV-2 induced macrophage activation syndrome in the setting of juvenile idiopathic arthritis.

Keywords: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Macrophage Activation Syndrome (MAS), secondary haemophagocytic lymphohistocytosis (sHLH), juvenile idiopathic arthritis (JIA)

Introduction: The pandemic of coronavirus disease-19 (COVID-19), caused by a new coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused significant morbidity and mortality worldwide.[1] An immune mediated hyper-inflammation in lungs seems to play an important role in development of acute respiratory distress syndrome, the main reason for morbidity and mortality in COVID-19.[2] Some laboratory parameters, highly suggestive of macrophage activation syndrome (MAS)/secondary haemophagocytic lymphohistiocytosis (sHLH) are also elevated in a subgroup of severe COVID-19 pneumonia cases. In those patients, a mimicry of autoimmune diseases may be seen including fever, arthralgia, myocarditis, cytopenias, coagulopathy and a cytokine storm similar to MAS.[3]

Secondary haemophagocytic lymphohistiocytosis occurs as a result of an exaggerated immunological reaction caused by different inciting conditions like infection, malignity or autoimmune diseases. MAS, as a form of sHLH, is usually associated with autoimmune rhemuatic disorders. It develops in approximately 7% of patients with juvenile idiopathic arthritis (JIA).[4]

A broad clinical spectrum affecting different organ systems may be seen over the course of COVID-19. Different clinical profiles may lead to diagnostic and therapeutic dilemmas in some complicated and overlapping conditions. Here, we present such a case; a child who developed MAS during in-hospital treatment of presumed septic arthritis with a differential diagnosis of JIA, and turned out to be SARS-CoV-2 positive.

Case report: A 10 year old boy had sufferred from right ankle pain, swelling and limping. After antibiotic therapy in another hospital, his complaints had partially resolved. Six weeks after the operation, he was admitted to our hospital with recurrence of pain, swelling of the right ankle, fever and refusal to walk. Swelling, redness, warmth and pain were noticed not

only on right ankle but also more manifestly on left knee. Acute phase reactants were increased (Table 1). Magnetic resonance imaging showed findings of arthritis and synovitis on affected joints. Aspiration of synovial fluid revealed 25500 leukocytes/microL with 86% of neutrophils. Although the overall clinical picture had features indicating a diagnosis of JIA, septic arthritis could not be excluded. Thence, an arthrotomy was performed for drainage and aspiration. No bacterial growth was observed on culture. Pathologic examination revealed chronic synovitis. Intravenous antibiotics was commenced, fever subsided, acute phase reactants decreased. The plan was 4 weeks of antibiotics for presumed septic arthritis, together with arrangement of treatment regarding JIA. On the 10^{th} day of hospitalization, he developed fever without any localizing signs and symptoms. No recurrence of arthralgia/arthritis was observed. Blood and urine cultures remained sterile. Viral serologic tests including Epstein barr virus and cytomegalovirus remained negative. Although there is no contact history, due to ongoing pandemic, a nasopharyngeal swab was taken for testing SARS-CoV-2 PCR on 4^{th} day of fever and found to be positive. Laboratory testing showed newly developed cytopenias, increased acute phase reactants, transaminases and trigylceride levels (Table 1). Bone marrow aspiration revealed abundant hemophagocytosis (Figure 1). Based on these findings, the patient was diagnosed as MAS in the setting of JIA, secondary to SARS-CoV-2 infection. Thorax CT, echocardiography and cardiac enzymes were normal. There were no signs and symptoms related to involvement of gastrointestinal, cutaneous and cardiovascular system. Favipiravir (loading dose: 1600 mg twice daily, maintenance dose:600 mg twice daily) was commenced for 5 days due to SARS-CoV-2 positivity in a child with MAS. For the treatment of MAS, 1 gr/kg/day intravenous immunoglobulin and plasma exchange were administered one after the other for 5 days and 10 mg/m^2/day dexamethasone was started. The patient's condition improved and all abnormal laboratory parameters

returned to normal levels. Steroid treatment was continued as oral methylprednisolone and methotrexate was planned as next step in the treatment of JIA.

Discussion:

Macrophage activation syndrome may be the first manifestation of sJIA, but it may also be seen during the course of an established JIA.[5] Viral infections are known triggers of MAS.[5-7] They can also execarbate an episode of MAS in patients with known autoimmune diseases.[6,7] Similarly, we believe that our patient with JIA has experienced a MAS episode, triggered by a viral infection, namely SARS-CoV-2.

A hyper-inflammatory state is known to occur in some COVID-19 patients. An exaggarated immune response resembling MAS/sHLH exacerbates the condition, which may end with mortality.[8] In COVID-19, this picture generally develops in conjuction with severe lung affection.[2] The patients with cytokine storm also have a severe COVID-19 pneumonia. This is somewhat different from the classic MAS associated with sJIA like settings, in which clinical manifestations generally occur outside the lungs. According to the 2016 MAS classification criteria, our case was diagnosed as MAS due to presence of fever, pancytopenia, increased transaminases, hyperferritinemia, low fibrinogen/high triglyceride levels and presence of hemophagocytosis.[9] He had no lung involvement and was in a relatively good condition throughout the course of the disease, unlike to what has been observed in cytokine storm related to COVID-19 pneumonia.

Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory condition associated with COVID-19. Although MAS and MIS-C have some features in common, they had also some distinct clinical and immunological characteristics.[10,11] MIS-C has been hypothesized as an immune-mediated postinfectious process to SARS–CoV-2, because the majority of patients have positive SARS-CoV-2 antibody, implying at least a duration of 1-2

weeks between acute infection and onset of MIS-C.[11] Klocperk et al described a child with a history of JIA who developed a feverish disease with multisystem involvement and systemic inflammation related to SARS-CoV-2 infection.[12] On contrary to our patient, this patient had severe gastrointestinal, cardiac and neurological involvement, a worse clinical status, seldom hemophagocytosis in the bone marrow, a lesser degree of increase in ferritin levels (577 μg/l), and virus-specific IgG positivity together with SARS-CoV-2 PCR positivity. Cardiac involvement, mucocutaneous changes and gastrointestinal symptoms, are reported to be characteristic fetaures of MIS-C rather than MAS.[13] Ferritin levels are found to be significantly higher in patients with MAS compared with MIS-C.[11] Thus, as the authors state, the patient developed a clinical picture compatible with MIS-C.[12]. There is neither previous history of COVID-19 exposure nor positive SARS-CoV-2 serology in our patient. He had no signs and symptoms of gastrointestinal, cardiovascular and/or mucocutaneous involvement. His clinical picture, as detailed previously, was compatible with a MAS episode rather than MIS-C.

Since there are conflicting evidence and recommendation surrounding high dose corticosteroid use especially in the early acute phase of COVID-19 infection, high dose steroid was not used in this case.[14] We made an immunomodulatory treatment plan so colled zipper method, which was previously used in the treatment of other immune-mediated diseases.[15] We think that early initiation of a comprehensive immunomodulatory treatment has helped to achieve a total clinical and laboratory response in a short time.

Small number of children with JIA have been reported to be infected with SARS-CoV-2, and in general low frequency of severe disease complications have been observed.[16,17] To our knowledge, this is the first case of SARS-CoV-2 induced MAS in the setting of JIA. The course of diagnosis and treatment was compelling due to many unknowns about this novel virus. It seems that SARS-CoV-2 has triggered a hyperinflammatory state in a backdrop of an

autoimmune disease. SARS-CoV-2 screening may be considered in flares of autoimmune diseases. We need guidance of accumulating experience and evidence regarding immunomodulatory and antiviral treatment options in such cases.

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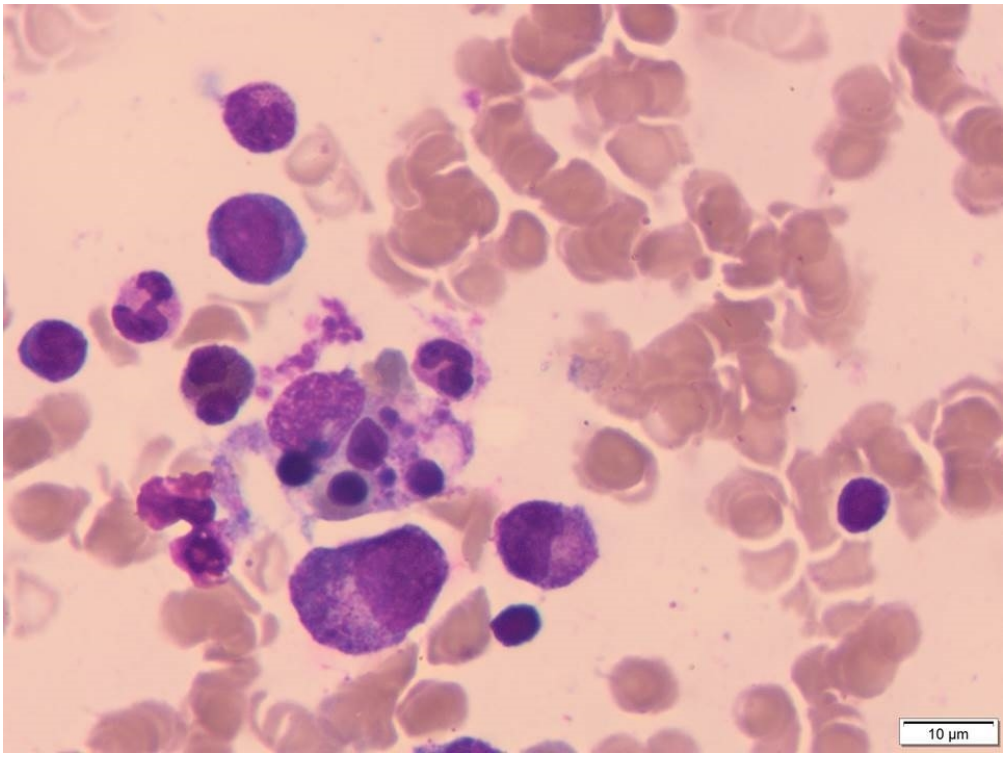
Table 1: Laboratory test results of the patient.

Laboratory tests	**On admission**	**On the day of diagnosis of MAS**
Leukocyte	16080 cells/mm^3	1750 cells/mm^3
Neutrophil	11700 cells/mm^3	1100 cells/mm^3
Lymphocytes	2400 cells/mm^3	500 cells/mm^3
Hemoglobin	10.5 g/dL	7.4 g/dL
Platelets	355000 cells/mm^3	75000 cells/mm^3
CRP (N:<5mg/dl)	192 mg/L	93 mg/dL
ESR	51 mm/hour	41 mm/hour
Procalcitonin	3,6 ng/ml	57 ng/mL
Ferritin (N:12-80 ng/mL),	-	6980 ng/mL
IL-6 (N:1,5-7 pg/mL).	-	23.6 pg/mL
D dimer (N:<500 ug/L),	-	>4000 ug/L
Fibrinogen	-	212 mg/dl
Triglyceride	-	174 mg/dl
Alanine aminotransferase (N:<39 U/L)	21 U/L	145 U/L
Aspartate aminotransferase (N:<52 U/L)	17 U/L	141 U/L
Lactate dehydrogenase (N:120-300 U/L)	-	696 U/L



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