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CASE REPORTS

MACROPHAGE ACTIVATION SYNDROME AFTER COVID-19 INFECTION IN A PATIENT WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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ABSTRACT

Macrophage activation syndrome is a serious, potentially fatal complication of the systemic form of juvenile idiopathic arthritis. It shares some common characteristics with the multisystem inflammatory disease in children, which is a late complication of SARS-CoV-2 infection in children.

We present an 11-year-old girl diagnosed with systemic juvenile idiopathic arthritis who has been diagnosed with macrophage activation syndrome soon after recovering from COVID-19 infection. The patient has developed pronounced thrombotic microangiopathy, a severe complication marked by significant drop in platelets, anaemia combined with low levels of haptoglobin, presence of schistocytes in blood smear, and new onset gross haematuria.

Keywords: *macrophage activation syndrome, juvenile idiopathic arthritis, thrombotic microangiopathy*

INTRODUCTION

Macrophage activation syndrome (MAS) is a serious, potentially fatal complication of some rheumatological diseases, most commonly a systemic form of juvenile idiopathic arthritis (sJIA), but can also manifest in patients with Kawasaki disease, systemic lupus erythematosus (SLE), and others (1,2). Macrophage activation syndrome has also been linked to some drugs (3,4) and sepsis (5). After the beginning of the SARS-CoV-2 pandemic, there was an increasing number of reports of children with MAS and MAS-like symptoms after COVID-19 infection (6,7). The exact prevalence of the syndrome is not yet established, but the connection with sJIA has been thoroughly studied and the occurrence of MAS in patients with this condition is considered to be between 10 and 50% (1,2).

The hallmark of MAS is the striking inflammatory response, caused by over-activation of T lymphocytes and macrophages and the subsequent cytokine storm. The exact mechanism that triggers MAS is still not clear, but there is evidence of cytotoxic dysfunction leading to the prolonged production of proinflammatory cytokines (1,8,9,10,11). Functional deficits and decreased number of natural killer (NK) cells that lead to failure to terminate the immune response also have been reported (12). There is increas-

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ing data of genetic malformations predisposing to hyperinflammatory state (13).

Macrophage activation syndrome is considered to be a secondary form of haemophagocytic lymphohistiocytosis (HLH) since both conditions share many similarities. However, there are differences both in pathogenesis and clinical course. That is the reason why a specific set of criteria for MAS was established (14,15). One of the most prominent symptoms of MAS is the nonremitting fever. Hepatomegaly and splenomegaly are usually present, and up to 35% of the patients develop neurological symptoms (16). From the laboratory parameters, aspartate and alanine aminotransferases, together with ferritin, lactate dehydrogenase, triglycerides, and d-dimer levels are increased. There is a sudden drop in the ESR levels or discrepancy between CRP and ESR, most probably caused by the hypofibrinogenaemia (16). One of the symptoms leading to increased mortality is thrombotic microangiopathy (17,18).

With the increased incidence of patients with SARS-CoV2 infection, a new disease entity was described – the multisystem inflammatory disease in children (MIS-C) (19). This condition is very similar to Kawasaki syndrome and has some common characteristics with MAS (20). The disease course is severe, but the outcome is much better than the one in patients with MAS.

CASE REPORT

We present an 11-year-old girl born from first normal pregnancy. Facial dysmorphic features, muscular hypotension, umbilical hernia, and developmental delay led to genetic testing at the age of 7 months, which showed ring chromosome 18. There was no family history of genetic or rheumatologic diseases.

She was first admitted to the clinic in October 2020 with fever, hepatosplenomegaly, lymphadenopathy, and arthritis, involving the elbow, knee, and ankle joints. Laboratory investigations showed increased inflammatory response, negative ANA and dsDNA-antibodies. Small pericardial effusion was found on echocardiography and she was diagnosed with systemic form of sJIA. She was started on methylprednisolone, 2 mg/kg per day, with careful dose weaning and methotrexate with a very good effect.

One month later she was hospitalised again with COVID-19 bilateral pneumonia. She was treated with antibiotics, IVIG, enoxaparine, and corticosteroids. After 12 days of treatment, her condition and the laboratory markers were normalised and she was discharged.

Two weeks later the girl became febrile with vomiting during the fever episodes. She looked pale the last couple of days and her urine became darker. A haemorrhagic rash appeared on the lower limbs and on the lips (Fig. 1). Complete blood count (CBC) showed anaemia and thrombocytopenia: Hb 6.5 g/dL, Thr 8 x 10^9/L. The girl was readmitted to our clinic in a deteriorated condition with fever, malaise, anaemia, haemorrhagic rash, and hepatosplenomegaly.

The blood investigations confirmed severe bicytopenia, with normal leucocyte count (9 x 10^9/L) and persistent lymphopenia. Biochemistry tests showed increased cholesterol levels (up to 10.11 mmol/L), increased LDH (5075 IU/L), increased liver enzymes (AST 124 IU/L, ALT 195 IU/L), ferritin (7610 ng/mL), and CRP (20 mg/L). Creatinine levels were increased up to 91 mcmol/L, BUN – up to 14.1 mcmol/L. To-

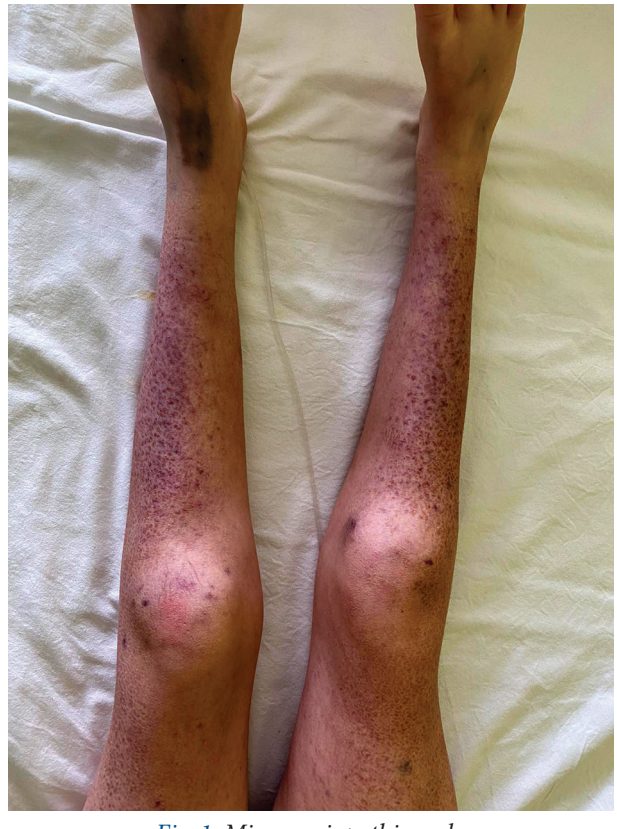

Fig. 1. Microangiopathic rash.

tal protein levels were moderately increased, cardiac enzymes were normal. Coagulation tests showed hypofibrinogenaemia (2.1…1.11 g/L), increased D-dimers (4.178 mg/L) and increased Factor VIII, von Willebrand factor, and von Willebrand factor antigen. There was macroscopic haematuria, proteinuria (0.899 g/L for 24-hour urine). GFR was decreased (64.9 mL/min/1.73).

Bone marrow aspiration two days after the hospitalisation showed erythroblastic dominance with signs of dyserythropoiesis and single macrophages without signs of hemophagocytosis. The second bone marrow biopsy was done on day 20, showing hypocellularity and equalization between the erythroid and myeloid lineages.

Immunological workup, including ANA, ENA, dsDNA-antibodies, pANCA and cANCA, anti-cardiolipin and anti-b2 glycoprotein antibodies, and immunoglobulins G and M showed no alterations. Coombs tests were negative. The panel for paroxysmal nocturnal haemoglobinuria (CD55 and CD59) was negative. The C3 levels were within the normal values, but C4 was low on the first and fourth day of the hospital admission and normalised on day 24. Cold agglutinins were persistently found. Multiple blood and urine cultures were negative. Flow cytometry highlighted the activation of cytotoxic CD3+, CD8+ and CD38+ T-lymphocytes, but the most striking finding was the complete lack of NK cells.

Ultrasound examination confirmed the hepato- and splenomegaly, additionally, small pericardial and pleural effusions were found. Chest X-ray showed no significant changes.

After a thorough discussion of different possible disease entities including MIS-C and Evans syndrome, it was concluded that the most probable diagnosis is MAS. The unusual findings, including the significant decrease of platelets, the striking anaemia combined with low levels of haptoglobin, the presence of schistocytes in blood smear, the high levels of urea and the new onset of gross haematuria, led to the conclusion that MAS was complicated with thrombotic microangiopathy (TMA).

The patient was treated in the intensive care unit (ICU) with methylprednisolone pulse therapy, IVIG 2 g/kg, and cyclosporin A with careful therapeutic drug monitoring. During the first two weeks of the disease course, the patient remained in critical condition, retaining severe bicytopenia, persisting fever, and highly increased inflammatory markers. She developed extreme hypertension and steroid diabetes due to the corticosteroid treatment, requiring treatment with subcutaneous insulin and oral antihypertensive drugs. After the resolution of the inflammatory response the persisting problem was the continuing hypercoagulation and microangiopathy with anaemia and thrombocytopenia, which improved after fresh frozen plasma infusions. Because of the critical condition of the patient, interleukin 1 inhibitor anakinra at a dose of 1 mg/kg daily was added to the therapy, resulting in improvement of the clinical condition and laboratory investigations. The girl was discharged with a recommendation for ongoing treatment with anakinra, cyclosporine, and methylprednisolone with a gradual dose reduction of the last two.

DISCUSSION

We report a case of a girl diagnosed with sJIA according to the International League of Associations for Rheumatology (ILAR) criteria (21). Treatment with methylprednisolone and methotrexate was started and the patient's condition dramatically improved. One month later she had to be readmitted because of a COVID-19 bilateral pneumonia and increased inflammatory markers. Shortly after being discharged from the hospital with a negative PCR test for COVID-19, the girl had to be hospitalised again with clinical and laboratory findings suggestive of severe inflammation and thrombotic microangiopathy.

The patient was diagnosed with MAS, as she covered the criteria for this condition (14,15). The most important underlying condition leading to this complication is the sJIA. However, there are multiple reports of young patients developing MAS secondary to viral infections, including the SARS-CoV2 infection (6,7). Up to date there are no laboratory markers or clinical signs that can differentiate the exact cause for this complication.

In addition, there is a new disease entity linked to COVID-19 – the multisystem inflammatory syndrome in children (MIS-C), which has a very similar disease course (19,20). The difficulty in this clinical case came from the similarities between the two syn-

dromes and the fact that the patient had predisposing factors that could lead to the manifestation of any of them. The findings that were common for both MAS and MIS-C were the critical condition that the patient was in, the acute kidney injury, and the fever. Furthermore, the girl presented with neutrophilia and lymphopenia (lymphopenia is more common in MIS-C), thrombocytopenia, high levels of LDH, increased D-dimers and very high levels of ferritin. The liver enzymes and cholesterol levels were also increased.

However, based on some symptoms and laboratory results, the diagnostic decision leaned towards MAS. This included the haemorrhagic rash, due to the extreme thrombocytopenia, instead of the typical macular efflorescence, characteristic for Kawasaki disease and MIS-C (14,15,19,20). The blood tests also showed low fibrinogen, one of the hallmarks of MAS. Although the fibrinogen levels could be low in MIS-C patients, it is more common for them to be increased. In addition, features such as the lack of myocardial involvement (unchanged troponin and normal ejection fraction on ultrasound) and the absence of pulmonary symptoms also pointed towards the diagnosis of MAS. Furthermore, there was no diarrhoea, respiratory symptoms, or swelling and desquamation of hands and feet (22). The haematological findings were also consistent with Evans syndrome (23), but the patient had additional symptoms, leading to other diagnoses, and the Coombs tests were negative.

We believe that our patient developed MAS after COVID-19 infection, complicated with TMA. This rare combination was first reported in a retrospective study from 2020 in 27 patients (18). The patients' clinical condition and laboratory values at TMA onset were comparable to those of our patient: 80.8% of the patients in the study had fever, 56% had hepatomegaly, 44% had splenomegaly, 96.3% had kidney involvement, and our patient presented with all these symptoms. The laboratory values from the study showed that the mean haemoglobin level at TMA onset was 8.1 g/dL, in our patient it was 6.5 g/dL, the mean platelet count in the study was 34 x 10^9/L, our patient's platelets were 16 x 10^9/L, mean fibrinogen in the study was 2.33 mg/L, in our case – 2.11 mg/L, mean ferritinin in study – 7.122 ng/mL, the ferritin level in our case was 7.610 ng/ml. The other laboratory values were also with changes similar to those of the patients in the study: elevated AST and LDH and low haptoglobin levels, our patient also had haematuria and schistocytes in blood smear.

CONCLUSION

In conclusion, the presented case demonstrates the difficulties in diagnosing a patient with MAS, mainly associated with the heterogeneous clinical picture and also the lack of pathognomonic diagnostic indicator. Moreover, with the rise of COVID-19 cases, it is important to differentiate between the symptoms of acute viral infection, and symptoms caused by MIS-C and MAS. The importance of fast and adequate treatment is of crucial value.

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