

Rheumatology key message

- TRAPS should be considered in patients presenting with recurrent, unexplained MAS, even in patients without a history of recurrent fever attacks.

**Dear Editor,**

Macrophage activation syndrome (MAS) is a life-threatening cytokine storm syndrome that results from the activation of T lymphocytes and hemophagocytic macrophages [1]. It can occur in the course of infections, malignancy, autoimmune diseases and rheumatic diseases [2]. Among rheumatic diseases, MAS is most commonly seen in systemic JIA. It can also develop in SLE, Kawasaki disease and autoinflammatory diseases. Typical clinical and laboratory findings are sustained fever, rash, hepatosplenomegaly, lymphadenopathy, hyperferritinaemia, pancytopenia, fibrinolytic consumptive coagulopathy, hypertriglyceridaemia and liver dysfunction [3].

TNF receptor–associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disease caused by mutations in the TNFRSF1A gene [3]. It is characterized by recurrent episodes of fever, rash, abdominal pain, periorbital oedema and arthralgia. MAS is rarely seen in TRAPS patients. Two cases have been reported in the literature. Herein we report a case of TRAPS presenting with MAS.

A 6-year-old female patient was admitted with intermittent fever for the last month. She had non-consanguineous healthy parents. The child did not have any history of recurrent fever attacks. Since she had leucocyturia in the urine examination, intravenous antibiotics were started with the provisional diagnosis of pyelonephritis and urosepsis. Blood and urine cultures were sterile. Extensive viral serology tests were all negative. After 2 weeks of treatment, the fever continued and she was referred to our clinic with the provisional diagnosis of multisystem inflammatory syndrome in children (MIS-C), as she had a history of coronavirus disease 2019 (COVID-19) infection 4 months earlier.

On physical examination there was no rash or joint findings suggestive of systemic JIA. Complete blood count showed anaemia (haemoglobin 8.8 g/dl) with normal leucocyte counts (5900/mm³) without lymphopenia and normal platelet counts (205,000/mm³). Acute phase reactants were mildly elevated [CRP 8.2 mg/l (normal 0–5), ESR 36 mm/h (normal 0–20)]. Urinalysis did not reveal any pyuria, haematuria or proteinuria. Other abnormal laboratory findings were hyperferritinaemia (ferritin 809 ng/ml (normal 13–150)), hypertriglyceridaemia [triglycerides 233 mg/dl (normal 0–150)] and aspartate aminotransferase was mildly elevated (58 U/l). A serum severe acute respiratory syndrome coronavirus 2 IgG antibody test was positive. The child was diagnosed as having MIS-C [4]. IVIG (2 g/kg) and corticosteroid therapy (2 mg/kg/day) were started. Echocardiography was normal.

On the third day of hospitalization, the fever continued, pancytopenia (haemoglobin 7.9 g/dl, leukocytes 2050/mm³, platelets 110,000/mm³) developed and ferritin increased to 2400 ng/ml. She was admitted to the paediatric intensive care unit (PICU). Plasmapheresis was started. In the bone marrow aspiration, haemophagocytosis was observed and the culture was sterile. Genetic tests for familial haemophagocytic lymphohistiocytosis (HLH) and periodic fever syndromes (including MEFV, MVK, NLRP3, TNFRSF1A) were performed. Dexamethasone, ciclosporin and etoposide treatment were started according to the HLH 2004 protocol. After etoposide treatment, pancytopenia became more prominent (haemoglobin 7.9 g/dl, leukocytes 380/mm³, platelets 37,000/mm³). Ciclosporin and etoposide treatments were discontinued. Dexamethasone treatment was switched to pulse methylprednisolone (30 mg/kg/day) and anakinra treatment was started. The fever regressed and cytopenia improved on the day 7 of anakinra. After 22 days of PICU follow-up, the patient was taken to the in-patient ward. During the follow-up, she did not have fever, and methylprednisolone treatment was gradually decreased. The patient was discharged with anakinra and methylprednisolone treatments.

No mutation was detected in the STX11 and PRF1 genes. In the UNC13D gene, homozygous c.2599A>G (p.K867E) sequence variation was detected, which was classified as a benign variation in the databases. In the follow-up, the patient had two more MAS attacks that were controlled by increasing the doses of methylprednisolone and anakinra. In the autoinflammatory disease gene panel, a heterozygous c.236C>T p.(Thr79Met) (T50M) mutation was detected in the third exon of the TNFRSF1A gene. This mutation was classified as pathogenic in the databases and the child had the final diagnosis of TRAPS and anakinra treatment was continued.

To the best of our knowledge, this is the third TRAPS case presenting with MAS. The first case of TRAPS and MAS reported in the literature was an 11-year-old girl who presented with MAS as the initial symptom [5]. In the follow-up of the patient, autoinflammatory disease was suspected due to ongoing recurrent fever attacks.
She was diagnosed with TRAPS and was treated with anakinra without attacks. The second case was a 9-year-old girl who presented with life-threatening MAS and neurological involvement [6]. She was treated with intravenous high-dose anakinra and was discharged with complete recovery.

MAS can be fatal if not detected early. It should be considered in patients with persistent fever and multi-organ involvement and early treatment should be started. MAS is a cytokine storm condition. The cytokines associated with MAS include IFN-γ, IL-1, IL-6, IL-12, IL-18 and TNF [1]. Anakinra is a recombinant human IL-1 receptor antagonist that blocks IL-1. Recently, especially after the COVID-19 period, its use has increased in MAS and secondary HLH, as it is less toxic and targeted than standard etoposide protocols. In the study of Eloseily et al. [7], anakinra was used in 44 patients with secondary HLH and early initiation of anakinra treatment was found to reduce mortality.

In conclusion, TRAPS should be considered in patients presenting with recurrent, unexplained MAS, even in patients without a history of recurrent fever attacks. In these patients, successful results are obtained with anti-IL-1 treatment.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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