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The Manifestations of Macrophage Activation Syndrome: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author MK wrote the draft of the manuscript. All Authors managed the literature searches. All authors designed the figures, managed literature searches and contributed to the correction of the draft. Authors ZM and MRH provided the case, the figures and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Macrophage Activation Syndrome (MAS) is a rare and life-threatening complication of various chronic rheumatic diseases. It is associated with systemic-onset juvenile idiopathic arthritis (SoJIA).
Case Report: A 19-year old woman was referred to our hospital with a history of fever, sweating, anorexia, and pancytopenia, due to her persistent fever; she was admitted in the infectious disease department. Bone marrow aspiration and biopsy findings were suggestive for MAS associated with SoJIA or Still's disease. She showed a remarkable response to treatment after Hydrocortisone and cyclosporine.

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Conclusion: MAS can occur within a few days after overt manifestations of the primary disease. Our patient developed MAS symptoms rapidly. MAS might be predictor to rheumatic diseases.

Keywords: Macrophage activation syndrome; systemic-onset juvenile idiopathic arthritis; still's disease; bone marrow biopsy; bone marrow aspiration.

1. INTRODUCTION

Macrophage Activation Syndrome (MAS) is a life-threatening complication of some chronic rheumatic diseases [1]. It is a rare syndrome which is commonly associated with systemic-onset juvenile idiopathic arthritis (SoJIA) or Still's disease. MAS can be fatal [2].

It also has been presented in adult-onset Still's disease, Systemic Lupus Erythematosus (SLE), Kawasaki disease and other non-rheumatic diseases. MAS is similar to reactive Hemophagocytic Lympho Histiocytosis (HLH) [3].

The main characteristic of MAS is the excessive activation and proliferation of T lymphocytes and macrophages. Hypercytokinemia, including high levels of interleukin, interferon and tumor necrosis factor occurs in MAS [4,5].

It is also characterized by high fever, hepatosplenomegaly, pancytopenia, encephalopathy, hepatic dysfunction, lymphadenopathy and intravascular coagulation [1,4].

MAS might be a direct result of infection, change in medication regimen or it might emerge simultaneously with active rheumatic diseases. Among children with rheumatic diseases, MAS occurs more often in SoJIA cases and is less frequent in other rheumatic diseases. Abnormality in the immune system might be the main mechanism of disease. It can contribute to losing control over an exaggerated immune response. However, this syndrome is not fully understood [4]. Some laboratory alterations might associate with MAS such as change in ferritin. Circulating ferritin might have a role in the development of autoimmune disease and inflammation [6].

This study aimed to report a successfully treated case of macrophage activation syndrome associated with systemic-onset juvenile idiopathic arthritis.

2. CASE REPORT

A 19-year old girl was referred to Imam Reza hospital (MASHHAD-IRAN) with a history of fever, sweating, anorexia and pancytopenia in 2013. She was admitted in the hematology department because of severe pancytopenia in 6 months later.

Her brother was previously admitted in this hospital with fever, pancytopenia, abdominal lymphadenopathy, lung nodules and pulmonary embolism in 2006. He was firstly diagnosed as a lymphoma case. Further investigations showed normal bone marrow aspiration (BMA), impaired liver function test (LFT) and high serum level of Lactate Dehydrogenase (LDH). He was expired during the treatment course in the same year.

Laboratory data during admission were summarized in Table 1. Laboratory data on as cites and plural fluid was shown in Table 2. Laboratory data of infectious and serologic factors are shown in Table 2.

2.1 Radiologic Findings

Chest X-ray of the patient was normal. Ultrasound findings revealed heterogeneous splenomegaly (250×77mm) with pelvic extension and hepatomegaly.

Contrast enhanced computed tomography scan (CT-scan) of the abdomen and pelvis showed a 300mm enlarged spleen with normal density and a few Paraaortic lymph nodes with 7-8mm diameter.

2.2 Bone Marrow Study

Bone Marrow Biopsy (BMB) showed Hypercellular bone marrow with evidence of dysplasia in erythroid and megakaryocytic traces. Although lymphoproliferative disease became one of the main differential diagnoses in this case, but it was role out with BMB findings. The obtained results showed active cellular marrow

Table 1. Laboratory data

Index	Level	Index	Level
Hemoglobin (Hb)	9.2 g/dl	Fibrinogen	127 mg/dL
White Blood Cell (WBC)	1500/ mm^3	TG	3000 mg/dL
Notrophil (PMN)	27%	Thyroglobulin (Tg)	24.7 µg/L
Lymphocite (LYM)	62%	Ferritin	2000ng/ml
Red Blood Cell (RBC)	3.5×10^6/µL	IgG	1355 mg/dl
Mean Corpuscular Volume (MCV)	82 fl	IgM	87 mg/dl
Platelet Count (PLT)	21000 /µl	IgA	80 mg/dl
Alkaline Phosphatase (ALP)	188IU/L	IgE	125 mg/dl
Aspartate Aminotransferase (AST)	17 U/L	ANA	0.2
Alanine AminoTranferease (ALT)	17U/L	Anti DNA	1.7 IU/ml
Lactate Dehydrogenase (LDH)	499U/L	ACE	302 g/w
Creatinine	0.6mg/dl	ANA	10/ml
Erythrocyte Sedimentation Rate (ESR)	20 mm/h	AntiDNA	14/ml
Anti smAb	Neg	HIV	Neg
Anti ssAAb	Neg	Anti scl70 Ab	Neg
Anti ssBAb	Neg	Anti jo_1	Neg
Borrelia	Neg	Anti RNP Ab	Neg
Malaria	Neg	EBV IgG	Neg
Leshme	Neg	CMV IgG	Neg

Table 2. Ascites and plural fluid

	Ascites fluid	Pleural fluid
Albumin	1200 mg/dl	-
Protein	1811 mg/dl	1463 mg/dl
White Blood Cell (WBC)	190 mm3	20 mm3
Notrophil (PMN)	20%	20%
Lymphocite (LYM)	80%	80%

With erythroid hyperplasia and mild dyserythropoiesis (Fig. 1).

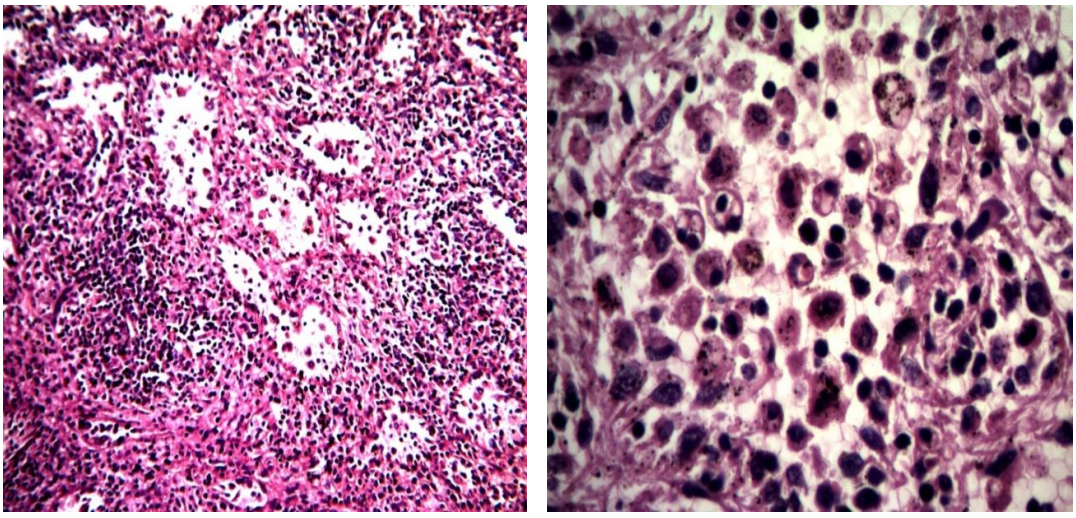
She underwent Splenectomy due to severe leukopenia (<1000) and thrombocytopenia (<2000). Histopathology investigations confirmed a congested spleen with hemophagocytic macrophage and extramedullary hematopoiesis (Fig. 2). Two weeks later she was readmitted with fever and thrombocytopenia. She received broad spectrum antibiotics despite negative blood and urine cultures. Fever had proceeded for over 10 days and she developed diffuse maculopapular rash on the chest and ankle arthritis. Triglycerides (TG) level and ferritin level (>2000) raised in this stage. MAS was proposed as a diagnosis for her, and she was treated with hydrocortisone 100 mg intravenously TDS, two weeks later her CBC was still abnormal and she had sever leukopenia (WBC: 1800 mm3), so, 200 mg/day cyclosporine was added to the regimen. She showed a fast response to this treatment approach and her general health improved and she was discharged from the hospital after 10 days.

3. DISCUSSION

We described a patient with clinical and laboratory features of Macrophage Activation Syndrome (MAS). MAS commonly occurs in juvenile idiopathic due to several chronic rheumatic diseases during childhood [7].

Identification, treatment and prevention methods of MAS are important because untreated MAS can be a life-threatening disease [2]. Despite new advantages in MAS, its pathogenesis is still remained unknown. It is proposed that T-helper (TH) response and cytokines secretion is distracted in these patients. These cytokines have a crucial role in macrophage activation and oxidative stress [7]. For instance TH17 has a regulatory role in inflammatory responses pathway on interleukin and tumor necrosis factor secretion which is correlated with various manifestation of MAS [4].

The question of whether MAS represents the most severe end of the spectrum of disease activity or it is a discrete clinical event is unclear. Many well-differentiated macrophages actively phagocytosis haematopoietic cells are disclosed in BMA(1). In addition, bone marrow, spleen, and lymph nodes are to be examined for any symptoms of MAS [2].



A B

Fig. 1. A. Spleen with dilated sinusoid contain macrophages (H&E.*40), B. Sinusoid of spleen with hemophagocytic macrophage (H&E*100)

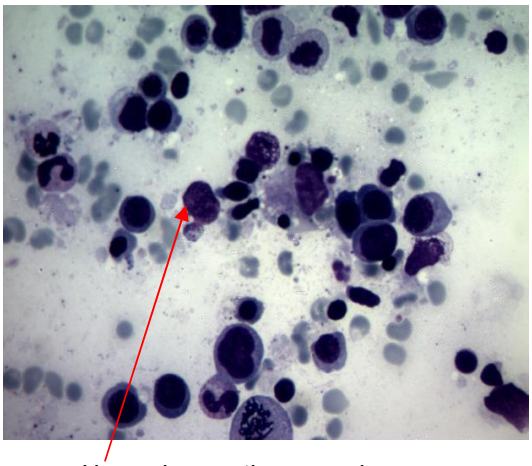


Fig. 2. Hemophagocytic macrophage, with erythroblast and platelet in cytoplasm (Bone Marrow biopsy), (MGG.*100)

In this study, we performed BMA smears and BMB to confirm MAS. Irregular release of inflammatory cytokines leads to the activation and uncontrolled proliferation of T-lymphocytes and macrophages [1].

Auto-immune disorders, systemic infection, or underlying malignancy might lead to MAS [2]. The diagnostic criteria of the International Registry consists of fever (seven or more days of a temperature as high as 38.5ºC), Splenomegaly, Cytopenia, Hypofibrinogenemia or Hypertriglyceridemia, Hemophagocytosis and rash. At least five of the criteria listed are necessary for accurate diagnosis [2]. Our patient showed many symptoms which were in accordance with the diagnostic criteria of MAS such as: persistent fever, sweating, anorexia, pancytopenia, diffuse maculopapular rash, ankle arthritis, high triglycerides level and high ferritin level.

The diagnosis of MAS is often a challenging issue as it might mimic a flare of the underlying disease. Our patient developed fever as the first sign of Macrophage Activation Syndrome.

Additionally, she had abnormal liver function tests which are a secondary cause to Macrophage Activation Syndrome [7,8].

The clinical presentation of MAS is similar to the SoJIA in many aspects. Furthermore, according to the obtained results of other studies, the abnormal Perforin expression and natural killer (NK) cells dysfunction might be related to the pathogenesis of MAS in soJRA [6].

The Behrens study reviewed the proposed pathogenesis of MAS/HIH. He showed the relationship of MAS with rheumatic disease such as systematic juvenile idiopathic arthritis (SJIA) [9]. However, its diagnosis can be difficult [10]. Clinically, there are strong similarities between Macrophage Activation Syndrome and familial and virus-associated reactive Hemophagocytic Lympho histiocytosis [6].

Lehmberg study was performed to identify measures distinguishing MAS in soJIA from Fusarium Heteropsprum Lipase (FHL) and VA-HLH and to define appropriate cutoff values. The results of that study discovered available measures which can rapidly differentiate between MAS/soJIA and FHL/VA-HLH. In addition, the decline of measures could facilitate the distinction of MAS from flares of soJIA [10].

Zeng et al. proved that MAS is a serious complication of JIA [11], as in our patient. It is also noteworthy that this study was consistent with that of Yeap et al. [12],Lehmberg et al. (Lehmberg), Shimizu et al. [13], Zeng et al. [14] and Rosário et al. [15].

There are some evidence about the efficacy of IL-1 receptor antagonist (IL1RA) (anakinra) in sJIA and Still's Disease [16]. It is estimated that more than 50% of patients with sJIA respond to IL1RA [16]. On the other hand some reports suggested it as a trigger for MAS [16]. We do not have IL1RA in Iran, so we treat our patient with cyclosporine. Administration of cyclosporine to in Yeap et al. study was similar to ours [12].

4. CONCLUSION

Our report clarified that MAS can occur within a few days of overt manifestations of the primary disease. The patient quickly developed MAS symptoms. Moreover, our report illustrates that MAS might be predictor to rheumatic diseases. Eventually, our patient successfully made a full clinical remission of MAS features.

CONSENT

All authors declare that 'written informed consent was obtained from the patient) for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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