Ref: Ro J Rheumatol. 2024;33(4)
DOI: 10.37897/RJR.2024.4.9

Atypical presentation of macrophage activation syndrome with extreme D-dimer elevation in juvenile systemic lupus erythematosus

Zahrah Hikmah[1,2], Melinda Masturina[1,2], Anang Endaryanto[1,2]

[1]Department of Child Health, Faculty of Medicine – Universitas Airlangga, Surabaya, Indonesia
[2]Department of Child Health, Dr.Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Macrophage Activation Syndrome (MAS) is a potentially life-threatening complication of juvenile systemic lupus erythematosus (jSLE), an uncommon but severe autoimmune disease in children. This case report presents a 7-year-old child newly diagnosed with jSLE who developed MAS, marked by persistent fever, abdominal pain, rash, cytopenia, elevated ferritin, hypertriglyceridemia, hypofibrinogenemia, and significantly elevated D-dimer levels. Diagnostic evaluation revealed low complement levels, positive antinuclear antibodies (ANA), and anti-double-stranded DNA (anti-dsDNA), confirming jSLE based on the SLICC classification criteria and MAS according to the EULAR/ACR criteria. Intensive therapy, including methylprednisolone, intravenous immunoglobulin, hydroxychloroquine, and anakinra, led to clinical improvement. This case underscores the unique occurrence of MAS in a patient at the initial diagnosis of jSLE, with an exceptionally elevated D-dimer. Clinicians should maintain a high level of vigilance for MAS in pediatric jSLE cases presenting with systemic inflammation and hematologic abnormalities, as prompt recognition and intervention are essential to improve outcomes.

Keywords: juvenile systemic lupus erythematosus, macrophage activation syndrome, pediatric autoimmune disease

Abbreviations (in alphabetical order):

ASTO	– anti-streptolysin O
EULAR	– European League Against Rheumatism
ESR	– erythrocyte sedimentation rate
FHLH	– familial hemophagocytic lymphohistiocytosis
jSLE	– juvenile systemic lupus erythematosus
MAS	– macrophage activation syndrome
SCD163	– soluble CD163
SCD25	– soluble interleukin-2 receptor alpha chain
SLE	– systemic lupus erythematosus
SLICC	– Systemic Lupus International Collaborating Clinics

INTRODUCTION

A chronic autoimmune multisystem inflammatory disease known as lupus can result in significant morbidity and mortality. Juvenile-onset systemic lupus erythematosus (jSLE) is the term for systemic lupus erythematosus that manifests in individuals under the age of 18. The annual incidence of jSLE is estimated at 0.3–0.9 per 100,000 children, with a prevalence of 3.3–24 per 100,000 children, which is a rare condition. Approximately 10% to 20% of patients with SLE receive their diagnosis during their adolescence. Juvenile SLE typically exhibits symptoms that worsen at a quicker rate than adult SLE due to its higher prevalence of complications such as lupus nephritis, hematologic disorders, photosensitivity, neu-

Corresponding author:
Zahrah Hikmah
E-mail: dr.zahrah.spa@gmail.com, dr.zahrah.hikmah@fk.unair.ac.id

Article History:
Received: 27 October 2024
Accepted: 4 December 2024

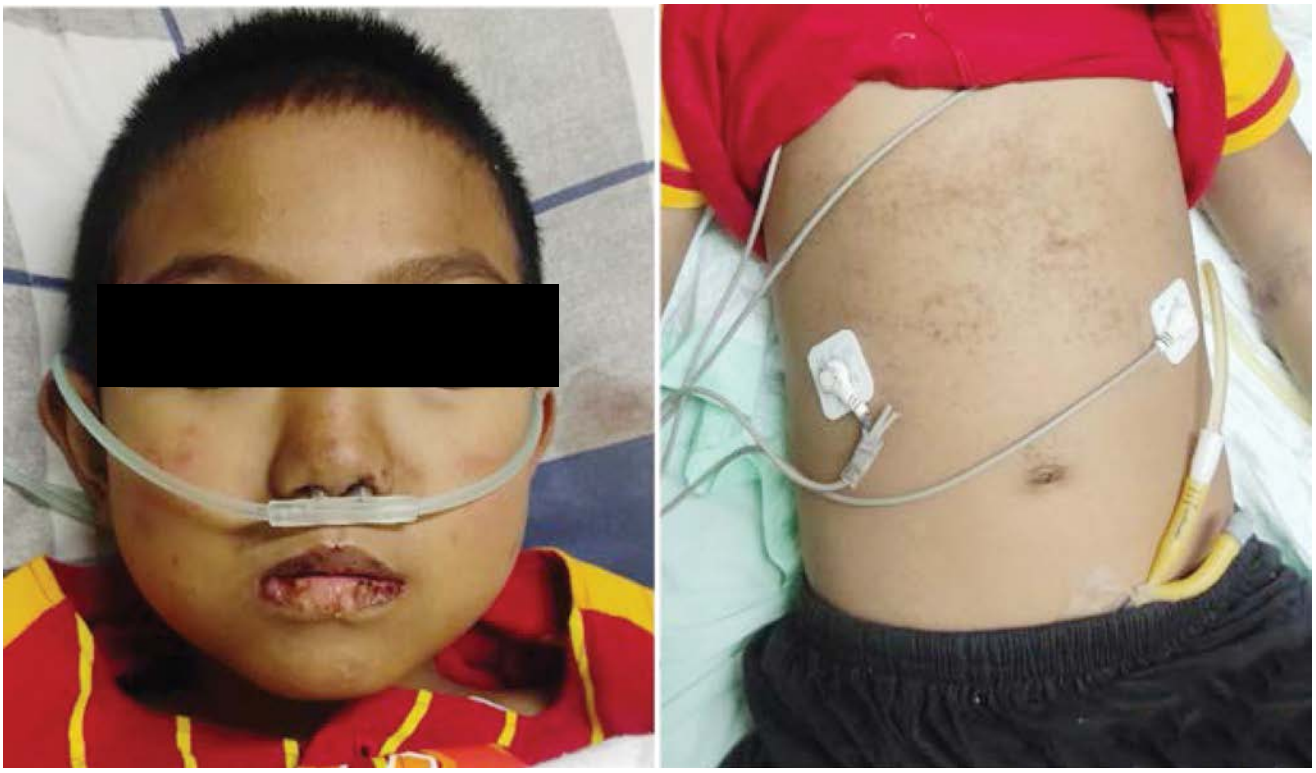

FIGURE 1. Rashes on the face and trunk

ropsychiatric symptoms, and mucocutaneous involvement [2].

One of the risks of a severe and potentially fatal illness, MAS, is a patient with SLE.

Macrophage Activation Syndrome (MAS) is a severe and potentially fatal complication in patients with SLE. MAS is a type of hemophagocytic lymphohistiocytosis (HLH), characterized by uncontrolled inflammatory cytokine production and systemic inflammation, leading to abnormal hemophagocytosis in multiple organs. The classification of MAS as a secondary or acquired HLH is the result of immunological factors, including innate immune dysfunction associated with the underlying rheumatic condition or iatrogenic immunosuppression. A genetic anomaly that impedes the cytotoxic function of T and NK cells is the primary cause of HLH [3].

The exact prevalence of MAS in patients with SLE is difficult to determine and is likely underestimated. Rapid and accurate diagnosis of MAS is particularly critical in pediatric SLE patients, as the estimated mortality rate exceeds 5%, significantly higher than the 0.2% observed in SLE children without MAS [4]. We present a case of MAS as an early manifestation of SLE in a child with extremely elevated D-dimer levels.

CASE REPORT

A 7-year-old patient presented with a persistent fever lasting 13 days, accompanied by abdominal pain, joint pain, and skin rashes. The patient had previously received treatment for typhoid fever at another hospital with intravenous ampicillin and ceftriaxone, yet no significant improvement was observed. Upon admission to our facility, the patient exhibited the following vital signs: hepatomegaly, palpable peripheral pulses, a facial and trunk rash (Figure 1), warm extremities, a heart rate of 126 beats per minute, a respiratory rate of 22 breaths per minute, blood pressure of 106/70 mmHg, and painful oral ulcers. All other systemic examination results were within normal limits.

Supportive treatment was initiated, including intravenous paracetamol and cefoperazone-sulbactam. Laboratory findings revealed a low white blood cell count, elevated ESR of 50 mm/hour, positive procalcitonin, and negative results for both rheumatoid factor and antistreptolysin O (ASTO). The laboratory data from the referring hospital were reviewed to corroborate these findings.

During the autoimmune evaluation on the second day, a positive ANA test result, positive anti-double stranded DNA (anti-dsDNA) antibody, decreased complement levels (C3 and C4), elevated interleukin-6, and an increased D-dimer level (10,500 ng/mL) were noted. A platelet count of 42,000/μL, indicating thrombocytopenia, was observed on the whole blood count, while urinalysis results were normal. Liver function tests showed elevated SGOT (108.8 U/L) and SGPT (16.11 U/L) levels. Procalcitonin, a marker of infection, rose to 2.42 ng/mL. Imaging revealed a pleural effusion on the right side, and abdominal ul-

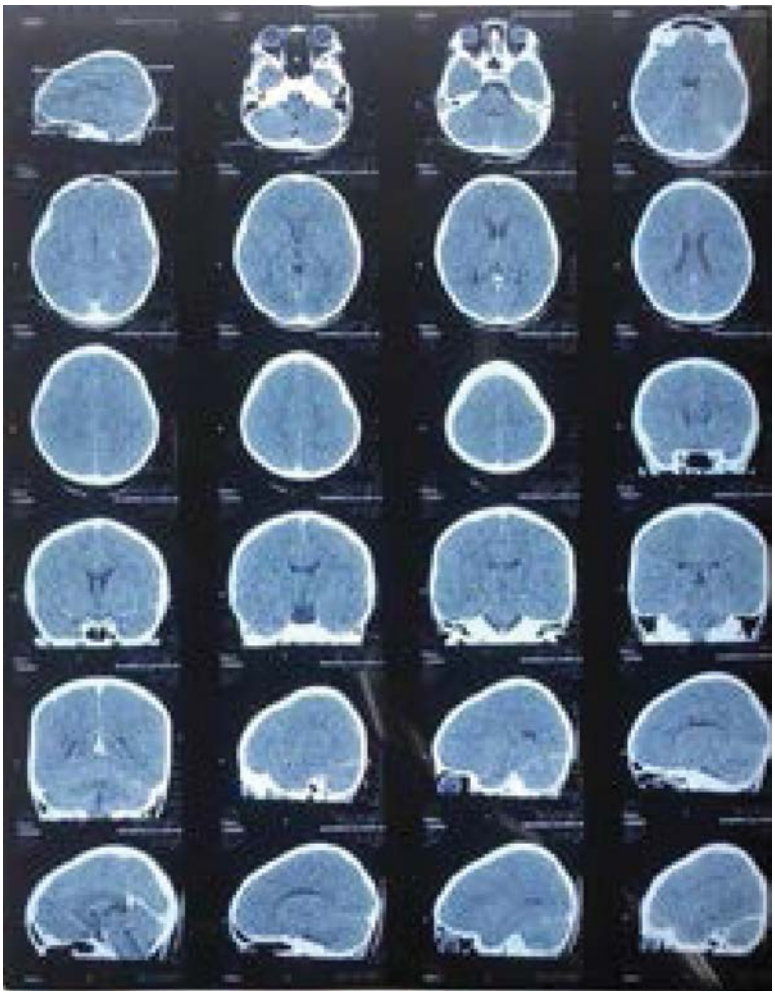

FIGURE 2. Head CT Scan

trasound showed no para-aortic lymph node enlargement, ascites, or hepatomegaly.

The diagnosis met five clinical and four laboratory criteria of the SLICC classification for systemic lupus erythematosus (SLE). A diagnosis of SLE with suspected macrophage activation syndrome (MAS) was established. The patient received a three-day course of methylprednisolone pulse therapy followed by oral hydroxychloroquine.

On the subsequent day, the patient's condition deteriorated. The fever persisted, abdominal pain worsened, and the child exhibited disorientation and delusions. Laboratory tests revealed a dramatically elevated D-dimer (88,500 ng/mL), increased ferritin (>1650 ng/mL), elevated triglycerides (186 mg/dL), and reduced fibrinogen (32.7 mg/dL). Lactate dehydrogenase levels were elevated (6337 U/L), and liver function tests showed significant increases (SGOT 3419.9 U/L, SGPT 1054.6 U/L). A head CT scan yielded normal findings (Figure 2).

The diagnosis of MAS was confirmed based on the EULAR/ACR criteria, and the patient was administered high-dose intravenous immunoglobulin and anakinra for treatment. Laboratory findings showed progressive improvement, the patient's clinical condition stabilized, and he was discharged from the hospital on a regimen of oral prednisone and oral hydroxychloroquine.

DISCUSSION

Macrophage Activation Syndrome (MAS) is a severe and potentially disastrous syndrome often linked to hemophagocytic lymphohistiocytosis (HLH). It is caused by excessive activation and multiplication of macrophages and T cells, culminating in a significant inflammatory response [11]. MAS is classified as a secondary variation of HLH. Genetic anomalies are the principal cause of primary HLH, impairing the ability of T and/or NK cells to eliminate target cells. The underlying cause of secondary or acquired HLH, including MAS, is immune system dysfunction. This may result from various factors, including immunosuppression due to medical therapy or dysfunction associated with underlying rheumatic illnesses. Individuals with rheumatic disorders may struggle to effectively eliminate infectious pathogens, primarily viruses, leading to the persistent activation of the immunological loop involving CD8+ T cells and macrophages. This uncontrolled systemic inflammation results in excessive synthesis of inflammatory cytokines, which may subsequently lead to dysregulated hemophagocytosis in various organs [5].

Hemophagocytosis is the primary mechanism behind the onset of MAS. This process involves the uptake and elimination of blood cells, including red blood cells, white blood cells, and platelets, by phagocytic cells. Macrophages engaged in hemophagocytosis are often associated with the development of MAS in individuals with systemic juvenile idiopathic arthritis (sJIA) and other rheumatologic conditions. Histological examination frequently reveals elevated hemophagocytic activity in the bone marrow, liver, and spleen, accompanied by significant CD163 staining in histiocytes. However, hemophagocytosis may not be immediately evident, making it an unreliable marker for MAS [6,7].

Laboratory techniques for detecting hemophagocytosis include measuring levels of soluble interleukin-2 receptor alpha chain (sCD25) and soluble CD163 (sCD163), a receptor with a strong affinity for hemoglobin-haptoglobin complexes. Elevated levels of these markers signify an improved capacity to identify MAS. These evaluations are conducted at specialized facilities, often incurring significant expenses

and causing delays, which may impede diagnosis and treatment. If overlooked, MAS can lead to multiple organ failure and potentially catastrophic outcomes [8].

Systemic Lupus Erythematosus (SLE) is a multifaceted autoimmune disorder that impacts various physiological systems and organs, resulting in diverse clinical presentations. Juvenile Systemic Lupus Erythematosus (jSLE), affecting individuals under 18 years of age, accounts for 10–20% of all SLE cases, with a prevalence ranging from 1.89 to 25.7 per 100,000 children, depending on ethnicity. Females are predominantly affected, with a gender ratio of 4–5:1 [9]. Juvenile SLE often exhibits a more severe clinical course than adult SLE, particularly with neurological and renal involvement. Additionally, SLE patients may develop MAS, which can result in multi-organ failure, enduring effects, and potentially fatal outcomes. Diagnosis is especially challenging in patients without a definitive diagnosis of a rheumatic illness. Common clinical signs of MAS include persistent high-grade fever resembling sepsis, hepatosplenomegaly, lymphadenopathy, and central nervous system impairment [10].

The principal symptoms of MAS include sustained fever, hyperferritinemia, pancytopenia, excessive fibrinolysis, and impaired liver function. A notable laboratory finding is significant hyperferritinemia. Large numbers of phagocytic macrophages ingesting hematological materials, indicative of MAS, are frequently observed in the bone marrow, liver, spleen, or lymph nodes. These macrophages can infiltrate and damage multiple organs, leading to the systemic manifestations associated with MAS [11].

The initial diagnosis of MAS relied on the diagnostic criteria for primary HLH, known as the HLH-2004 classification system. These criteria encompass clinical, laboratory, and histopathologic features, including fever, splenomegaly, cytopenia, elevated triglyceride and fibrinogen levels, diminished NK cell activity, elevated ferritin levels, increased soluble IL-2 receptor levels, and hemophagocytosis. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) established validated diagnostic criteria for MAS in individuals with juvenile idiopathic arthritis (JIA). However, no standardized criteria currently exist for diagnosing MAS in other juvenile rheumatic diseases, such as jSLE. As a result, the EULAR/ACR criteria are often applied in various clinical contexts, although their reliability for illnesses other than sJIA remains uncertain [12].

The EULAR/ACR established a validated diagnostic criterion for MAS in patients with systemic juvenile idiopathic arthritis (sJIA). According to these criteria, MAS in patients with sJIA is diagnosed in the presence of fever, elevated ferritin levels (>684 ng/ml), and at least two of the following: 1. a platelet count under 181; 2. aspartate aminotransferase (AST) >48 U/L; 3. triglycerides >156 mg/dL; and 4. fibrinogen <360 mg/dL. In 2016, a group of experts established diagnostic criteria that accurately differentiate between a flare of systemic juvenile idiopathic arthritis (sJIA) and MAS. The established criteria for children with systemic juvenile idiopathic arthritis (sJIA) demonstrate high sensitivity (0.73) and specificity (0.99). It might be diagnosed in a patient with systemic juvenile idiopathic arthritis (sJIA) who presents with fever and a serum ferritin level exceeding 684 ng/mL, along with at least two of the following criteria: a platelet count of 181×10^9/L, aspartate aminotransferase (AST) >48 U/L, triglycerides >156 mg/dL, or fibrinogen ≤360 mg/dL [6,13].

Owing to the clinical similarities between MAS and secondary HLH, numerous practitioners choose to use the established HLH-2004 diagnostic criteria. These guidelines specify that a diagnosis requires meeting at least five of the following eight criteria: fever, splenomegaly, cytopenias (involving two or more of the following: hemoglobin <90 g/L, platelets $<100 \times 10^9$/L, neutrophils $<1.0 \times 10^9$/L), elevated triglycerides (≥265 mg/dL) and/or reduced fibrinogen (≤1.5 g/L), evidence of hemophagocytosis in the bone marrow, spleen, or lymph nodes, diminished or absent natural killer (NK) cell activity, ferritin levels ≥500 µg/L, and sCD25 levels ≥2,400 U/mL. Enforcing these stringent criteria may result in delayed detection of patients with less severe initial presentations [14,15].

The MAS is associated with several rheumatic illnesses and is more prevalent in the systemic subtype of juvenile idiopathic arthritis (JIA). It is characterized by a class of histiocytic illnesses known as hemophagocytic lymphohistiocytosis (HLH). This condition encompasses a range of disorders marked by the accumulation of well-differentiated mononuclear cells with a macrophage phenotype. Since macrophages are a specific subtype of histiocytes, distinct from Langerhans cells, it is essential to differentiate MAS from Langerhans cell histiocytosis and other dendritic cell-related disorders. Histiocytic disorders are categorized into two main types: primary or familial hemophagocytic lymphohistiocytosis (FHLH) and secondary or reactive hemophagocytic lymphohistiocytosis (ReHLH) [16].

Differentiating between the two can be challenging. Familial HLH consists of a collection of rare immunological disorders inherited in an autosomal recessive manner. These diseases arise from genetic mutations in multiple genes that collectively affect the cytolytic pathway. Clinical signs typically manifest within the first two months of life [17]. The clinical progression of HLH is marked by persistent fever and hepatosplenomegaly. Neurological symptoms

can complicate and often dominate the clinical course. Hemorrhagic rash and lymphadenopathy occur less frequently. Test results typically reveal a combination of decreasing blood cell counts (particularly a reduced platelet count), elevated liver enzymes, hypertriglyceridemia, hyperferritinemia, and hypofibrinogenemia. These findings are similar to those seen in MAS. Like MAS, the presence of hemophagocytosis in the bone marrow is a distinguishing characteristic of HLH [18].

The MAS is characterized by considerable diagnostic difficulties that may result in delayed identification and/or insufficient acknowledgment of this disorder. The presence of a persistent and/or septic-like fever, along with concomitant clinical manifestations such as hepatosplenomegaly and lymphadenopathy, may suggest a diagnosis of MAS. Nonetheless, the emergence of MAS before the diagnosis of jSLE can obstruct the prompt identification of the condition [19]. It frequently presents during the onset of juvenile systemic lupus erythematosus (jSLE). It is crucial to evaluate specific criteria for diagnosing MAS in diverse rheumatic conditions. For jSLE, criteria specifically established for patients already diagnosed with the disease appear to be more effective than the ACR/EULAR criteria for sJIA-related cases, due to a lower ferritin threshold. This is also true for patients diagnosed with jSLE following an episode of MAS as the earliest manifestation of the illness [20]. The literature does not explicitly address the correlation between MAS and markedly elevated D-dimer levels in jSLE. However, D-dimer, a fibrin degradation product, is generally elevated in conditions associated with thrombosis and fibrinolysis, potentially arising from the hyperinflammatory state in MAS. Hyperferritinemia and hyperinflammation in MAS may theoretically create a prothrombotic state, leading to elevated D-dimer levels. Nevertheless, this link has not been clearly defined [21,22].

Increased D-dimer levels are often associated with various thrombotic and fibrinolytic disorders. In severe hyperinflammatory conditions, such as MAS, elevated D-dimer levels may indicate secondary coagulopathy resulting from increased fibrinolysis. This corresponds with the systemic activation of the coagulation cascade [23,24]. Elevated D-dimer levels are a common finding in MAS, but the literature does not uniformly investigate this parameter across all studies. This omission suggests that while D-dimer is a pertinent marker, it may not be the primary focus of all MAS-related research or may not demonstrate a distinctive increase in MAS compared to other types of HLH. In MAS, elevated D-dimer levels likely reflect the hypercoagulable state and secondary coagulopathy associated with the cytokine storm and systemic inflammation characteristic of this disorder [25–27].

CONCLUSION

In conclusion, this case highlights the uniqueness of MAS occurring in a patient newly diagnosed with jSLE, accompanied by exceptionally elevated D-dimer levels. While D-dimer is not routinely emphasized in the diagnosis of MAS, its extreme elevation in this case underscores its potential significance. Clinicians should remain vigilant for MAS in jSLE cases presenting with fever, cytopenia, and liver dysfunction, as prompt diagnosis and intensive therapy are crucial for improving outcomes. The diagnostic process in this study adhered to established criteria, with jSLE confirmed using the SLICC classification and MAS diagnosed based on the EULAR/ACR criteria. Further studies are needed to explore the role and pathophysiological implications of elevated D-dimer levels in MAS associated with jSLE.

Patient consent:
Written informed consent was obtained from the patient (or legal guardian) for publication of this case report.

Conflict of interest:
The authors declare no financial interest or conflict of interest related to this case report.

Authors' contributions:
Conceptualization, ZH and MM; methodology, ZH; validation, ZZ, MM, AE; formal analysis, ZZ, AE; investigation, ZH, AE; resources, ZZ, MM; data curation, ZH; writing—original draft preparation, ZH, MM, AE; writing—review and editing, ZZ, HH, AE; visualization, MM; supervision, AE; project administration, MM.
All authors have read and agreed to the published version of the manuscript.

Acknowledgments:
The authors thank the Faculty of Medicine, Airlangga University, and the Child Health Department, Dr. Soetomo General Hospital, for their support in this study.

REFERENCES

1. Harry O, Yasin S, Brunner H. Childhood-Onset Systemic Lupus Erythematosus: A Review and Update. *J Pediatr.* 2018;196:22-30. e2. doi: 10.1016/j.jpeds.2018.01.045.
2. Kumar P, Prasad A, Patra PK, Fadila. Childhood-onset systemic lupus erythematosus in the first year of life with joint involvement: A case report and mini-review. *J Family Med Prim Care.* 2022;11:6571. doi: 10.4103/jfmpc.jfmpc_569_22.
3. Cowley S, Ramakrishnan S. Macrophage activation syndrome in a patient with systemic lupus erythematosus. *Pol Arch Intern Med*. 2019;129:535-8. doi: 10.20452/pamw.14953.
4. Abdirakhmanova A, Sazonov V, Mukusheva Z, Assylbekova M, Abdukhakimova D, Poddighe D. Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus: A Systematic Review of the Diagnostic Aspects. *Front Med* (Lausanne). 2021;8:681875. doi: 10.3389/fmed.2021.681875.
5. Henderson LA, Cron RQ. Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management. *Paediatr Drugs.* 2020;22(1):29-44. doi: 10.1007/s40272-019-00367-1.
6. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. *Front Immunol.* 2019;10:119. doi: 10.3389/fimmu.2019.00119.
7. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. *Annu Rev Pathol.* 2018;13(1):27-49. doi: 10.1146/annurev-pathol-020117-043625.
8. Awasthi S, Upreti S. Macrophage activation syndrome in a patient with systemic lupus erythematosus (SLE) and dual viremia. *J Community Hosp Intern Med Perspect.* 2020;10(5):470-4. doi: 10.1080/20009666.2020.1787811.
9. Sahin S, Adrovic A, Barut K, Canpolat N, Ozluk Y, Kilicaslan I, et al. Juvenile systemic lupus erythematosus in Turkey: demographic, clinical and laboratory features with disease activity and outcome. *Lupus*. 2017;27:514-9. doi: 10.1177/0961203317747717.
10. Aziz A, Castaneda EE, Ahmad N, Veerapalli H, Rockferry AG, Lankala CR, et al. Exploring Macrophage Activation Syndrome Secondary to Systemic Lupus Erythematosus in Adults: A Systematic Review of the Literature. *Cureus*. 2021;13. doi: 10.7759/cureus.18822.
11. Eloseily EM, Cron RQ. Macrophage Activation Syndrome. Springer eBooks. 2018;151-82. doi: 10.1007/978-3-319-79026-8_14.
12. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. *Open Access Rheumatol*. 2018;10:117-28. doi: 10.2147/OARRR.S151013.
13. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. *Blood Res.* 2021;56(S1). doi: 10.5045/br.2021.2020323.
14. La Rosée P, Horne A, Hines M, Von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133:2465-77. doi: 10.1182/blood.2018894618.
15. Rolsdorph LÅ, Mosevoll KA, Helgeland L, Reikvam H. Concomitant Hemophagocytic Lymphohistiocytosis and Cytomegalovirus Disease: A Case Based Systemic Review. *Front Med.* 2022;9:819465. doi: 10.3389/fmed.2022.819465.
16. Carter S. Macrophage Activation Syndrome: An Update And Practical Approach. Clinical Cases 1 And 2: Macrophage Activation Syndrome In Rheumatology Practice. *Rheumatology*. 2017;56(Suppl_2). doi: 10.1093/rheumatology/kex060.089.
17. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, et al; Paediatric Rheumatology International Trials Organisation; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis.* 2016 Mar;75(3):481-9. doi: 10.1136/annrheumdis-2015-208982.