Atypical presentation of macrophage activation syndrome with extreme d-dimer elevation in juvenile Systemic Lupus Erythematosus

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Atypical presentation of macrophage activation syndrome with extreme d-dimer elevation in juvenile Systemic Lupus Erythematosus

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ABSTRACT

Juvenile systemic lupus erythematosus (jSLE) is a rare yet severe autoimmune disorder in children, with potentially fatal complications like Macrophage Activation Syndrome (MAS). We report a 13-year-old with jSLE presenting with fever, abdominal pain, rashes, and extreme D-dimer elevation, indicating MAS. Immunological workup showed positive ANA, anti-dsDNA, and low complement. Intensive treatment with methylprednisolone, hydroxychloroquine, and anakinra improved the patient's condition. This case emphasizes the diagnostic challenge of MAS in jSLE and the need for prompt intervention in similar pediatric cases.

Keywords: Juvenile Systemic Lupus Erythematosus, Macrophage Activation Syndrome, Pediatric autoimmune disease

Abbreviations:

jSLE - Juvenile Systemic Lupus Erythematosus

SLE - Systemic Lupus Erythematosus

MAS - Macrophage Activation Syndrome

ASTO - Anti-Streptolysin O

ESR - Erythrocyte Sedimentation Rate

SLICC - Systemic Lupus International Collaborating Clinics

EULAR - European League Against Rheumatism

sCD25 - Soluble Interleukin-2 Receptor Alpha Chain

sCD163 - Soluble CD163

FHLH - Familial Hemophagocytic Lymphohistiocytosis

INTRODUCTION

The autoimmune multisystem inflammatory illness known as lupus is a chronic condition that can cause significant morbidity as well as death. Lupus that manifests in a person younger than 18 years of age is known as juvenile-onset systemic lupus erythematosus (jSLE). jSLE is uncommon, with reported incidences of 0.3–0.9 per 100,000 children annually and prevalences of 3.3–24 per 100,000 children [1]. There are 10% to 20% of SLE patients who receive their diagnosis when they are young. When compared to adult SLE, juvenile SLE usually exhibits a more severe clinical course, with a higher incidence of lupus nephritis, hematologic abnormalities, photosensitivity, neuropsychiatric involvement, and mucocutaneous involvement [2].

Patients with systemic lupus erythematosus (SLE) are at risk of developing a serious and potentially fatal condition, known as Macrophage Activation Syndrome (MAS). MAS is a form of hemophagocytic lymphohistiocytosis (HLH), which is characterized by uncontrolled systemic inflammation and massive production of inflammatory cytokines, leading to dysregulated hemophagocytosis in multiple organs. MAS is considered a secondary or acquired HLH, which results from immunological causes such as innate immune dysfunction associated with the underlying rheumatic disease or iatrogenic immunosuppression. The main cause of Primary HLH is a genetic abnormality that impairs the cytotoxic activity of T and NK cells [3].

It is difficult to determine the exact prevalence of MAS in patients with SLE, but it is believed to be underestimated. Early and accurate diagnosis of MAS is critical, especially in pediatric patients with SLE, as the estimated mortality rate is approximately 5%, which is significantly higher than that in patients with SLE without MAS (0.2%) [4]. In this case report, we present an SLE patient with an extremely elevated D-dimer level, which was the first sign of MAS

CASE REPORT

A 13-year-old patient presented with persistent fever for 13 days and stomach pain, along with joint pain and skin rashes. The individual had previously received IV ampicillin and ceftriaxone treatment for typhoid fever at another hospital, without showing clinical improvement. Upon admission to our hospital, the child's vital signs were: fever (39oC), heart rate (126 bpm), respiration rate (22/min), blood pressure (106/70), warm extremities, facial and trunk rash (see Figure 1), painful oral ulcers, palpable peripheral pulses, hepatomegaly, and normal findings on other systemic examination. The patient was initiated on supportive therapy, including inj. Cefaperazole-sulbactam and paracetamol. Laboratory results from the previous hospital revealed leukopenia, elevated ESR (50), positive procalcitonin and rheumatoid factor, negative ASTO, and positive IgM salmonella

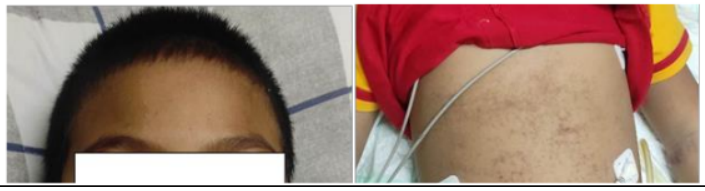

Figure 1. Rashes in face and trunk

On the second day, the autoimmune work-up examination revealed positive for ANA test (185), positive for anti-ds-DNA (52.5), elevated levels of anti-SRBD (12.23), and lowered levels of complement C3 (43) and C4 (5.5), Il-6 was increased,. The was increasing of D-dimer (10.500). The complete blood count revealed thrombocytopenia, with a platelet count of 42000. The urinalysis results were within the normal range. The liver function test showed elevated levels of SGOT (108,8) and SGPT (16,11). There was an increase in infection marker procalcitonin (2.42). There was presence of a pleural effusion on the right side. An abdominal ultrasound showed hepatomegaly, ascites, and no paraaortic lymph node enlargement. The SLICC classification criteria for systemic lupus erythematosus was fulfilled with 5 clinical criteria and 4 laboratory criteria. Systemic lupus erythematosus was established and suspicion of Macrophage Activation Syndrome. The patient was treated with methylprednisolone pulse 3 day consecutively and hydroxichloroquin orally.

In next day, the condition of child was deteoriated, a persistent fever, intense abdominal pain, and child becomes disoriented and develops delusions. Laboratory revealed increased (88,500), increased liver function test (SGOT 3419,9 SGPT 1054,6), increased Lactat dehidrogenase (6337),hyponatremia (129) and Head CT scan revealed normal. (figure 2)

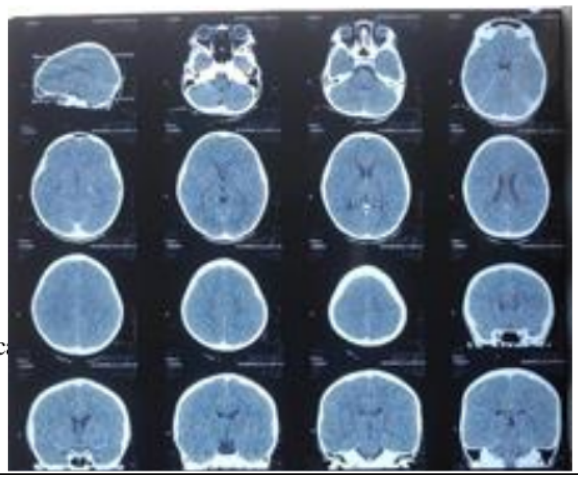

Figure 2. Head CT Sc

The child was treated with high dose intravenous immunoglobulin and Anankira. After all the treatment, the clinical condition was better, laboratory gradually better and patient discharged from hospital with treatment oral prednison and oral hidroxycloroquin

DISCUSSION

Macrophage activation syndrome (MAS) is a severe medical disorder that is often linked to hemophagocytic lymphohistiocytosis (HLH). MAS is a grave and potentially disastrous disease that arises from the excessive activation and multiplication of macrophages and T cells, culminating in a severe inflammatory reaction (Eloseily, 2018). MAS is classified as a secondary form of hemophagocytic lymphohistiocytosis (HLH). Genetic disorders are the main cause of primary HLH, which impairs the ability of T and/or NK cells to eliminate target cells. The primary pathogenic event in secondary or acquired HLH or MAS is an immunological element, which can occur due to a combination of factors such as iatrogenic immunosuppression and/or inherent immune dysfunction associated with the underlying rheumatic illness. In patients with rheumatic conditions, the inability to effectively remove infectious organisms, usually viruses, can lead to the ongoing activation of the immunological loop involving CD8+ T cells and macrophages. This can result in uncontrolled systemic inflammation and excessive synthesis of inflammatory cytokines, which in turn causes dysregulated hemophagocytosis in many organs [5].

Hemophagocytosis serves as the primary mechanism for the development of MAS. This process involves the engulfment and consumption of blood cells, including red blood cells, white blood cells, and platelets, by phagocytic cells. Macrophages that participate in hemophagocytosis are commonly associated with the development of macrophage activation syndrome (MAS) in individuals with systemic juvenile idiopathic arthritis (sJIA) and other rheumatologic diseases. Histological examination frequently reveals heightened hemophagocytic activity in the bone marrow, liver, and spleen, accompanied by intense CD163 staining in histiocytes. However,

hemophagocytosis may not be immediately detectable and can be an unreliable marker for MAS [6,7].

Laboratory tests for detecting hemophagocytosis involve measuring the levels of soluble interleukin 2 receptor alpha chain (sCD25) and soluble CD163 (sCD163), a receptor that strongly binds to hemoglobin-haptoglobin complexes. Elevated levels of these indicators suggest a greater capacity to identify macrophage activation syndrome (MAS). These tests are conducted at designated facilities, resulting in significant expenses and prolonged waiting times for results, which can delay diagnosis and treatment. If left untreated, MAS can lead to the failure of multiple organs and potentially result in fatal outcomes [8].

Systemic Lupus Erythematosus (SLE) is an intricate autoimmune disorder that can have an impact on a wide range of bodily systems and organs, resulting in a diverse array of clinical symptoms. Pediatric Systemic Lupus Erythematosus (pSLE), which affects individuals under the age of 18, accounts for 10-20% of all SLE cases with a prevalence rate ranging from 1.89 to 25.7 per 100,000 children, depending on the ethnic group. Females are more commonly affected, with a gender ratio of 4-5:1 [9]. The condition often exhibits a more severe clinical course in comparison to adult SLE, particularly in relation to neurological and renal symptoms. Additionally, SLE patients may develop Macrophage Activation Syndrome (MAS), which can result in several organ-related and long-term consequences, in addition to potentially fatal outcomes. MAS can be difficult to diagnose, especially when it presents in individuals without a definitive diagnosis of a rheumatic condition. Common clinical symptoms of MAS include continuous high-grade fever resembling sepsis, enlargement of the liver and spleen, swelling of the lymph nodes, and malfunction of the central nervous system [10].

The primary symptoms of MAS consist of prolonged fever, elevated levels of ferritin in the blood, reduced counts of all types of blood cells, excessive breakdown of blood clots, and impaired liver function. Another notable laboratory discovery is the presence of striking hyperferritinemia. The presence of a large number of distinct macrophages engulfing hematological materials, which is a characteristic sign of MAS, is frequently observed in the bone marrow, liver, spleen, or lymph nodes. The hemophagocytic macrophages have the ability to invade and affect practically every

organ in the body, perhaps causing many of the systemic characteristics associated with this condition [11]. The initial diagnosis of MAS relied on the diagnostic criteria established for primary HLH, known as the HLH-2004 classification system. These criteria encompass clinical, laboratory, and histopathologic findings, such as fever, splenomegaly, cytopenia, abnormal levels of triglycerides and fibrinogen, impaired NK cell function, elevated ferritin levels, increased soluble IL-2 receptor levels, and evidence of hemophagocytosis. The European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR) collaborated to create a set of guidelines for diagnosing MAS in patients with JIA. Currently, there are no established diagnostic criteria specifically for other pediatric rheumatic diseases, such as pSLE, to identify MAS. As a result, clinicians often use the EULAR/ACR criteria in different clinical settings to diagnose MAS. However, it remains uncertain whether these criteria can be reliably and accurately applied to diseases other than JIA [12].

The EULAR/ACR established a validated set of diagnostic criteria for macrophage activation syndrome (MAS) in patients with systemic juvenile idiopathic arthritis (sJIA). According to these criteria, MAS can be diagnosed in a febrile patient with confirmed or suspected sJIA if they have elevated blood ferritin levels (>684 ng/ml) and meet at least two of the following criteria: (1) platelet count less than 181*10^9/l, (2) aspartate aminotransferase is greater than 48 U/l, (3) triglycerides > 156 mg/dl, and (4) fibrinogen level < 360 mg/dl. In 2016, a group of experts released a set of diagnostic criteria proven to accurately differentiate between a flare of systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS). The ultimate criteria for children with systemic juvenile idiopathic arthritis (sJIA) shown high sensitivity (0.73) and specificity (0.99). MAS can be diagnosed in a patient with systemic juvenile idiopathic arthritis (sJIA) who has fever and a serum ferritin level higher than 684 ng/ml, along with two of the following: a platelet count of 181 × 109/l or lower, aspartate aminotransferase level higher than 48 units/l, triglyceride concentration higher than 156 mg/dl, or fibrinogen level of 360 mg/dl or lower [6,13].

Due to the clinical similarities between MAS and secondary HLH, some clinicians choose to use the well-established HLH-2004 diagnostic guidelines. These guidelines require the presence

of at least five out of the following eight criteria for a diagnosis: fever, enlarged spleen, cytopenias (involving two or more of the following: hemoglobin < 90 g/l, platelets < 100 × 109/l, neutrophils < 1.0 × 109/l), high levels of triglycerides (≥265 mg/dl) and/or low levels of fibrinogen (≤ 1.5 g/l), evidence of hemophagocytosis in the bone marrow, spleen, or lymph nodes, reduced or absent natural killer (NK) cell activity, ferritin levels ≥ 500 µg/l, and sCD25 levels ≥ 2,400 units/ml. Applying these stringent criteria may result in a delay in diagnosing patients who have a less severe first appearance [14,15].

MAS can be associated with several rheumatic illnesses, and it is more prevalent in the systemic subtype of juvenile idiopathic arthritis (JIA). MAS shares similarities with a group of histiocytic illnesses called hemophagocytic lymphohistiocytosis (HLH). HLH refers to a range of disease processes characterized by the buildup of well-differentiated mononuclear cells with a macrophage phenotype. Because macrophages are a specific type of histiocyte different from Langerhans cells, it is important to differentiate this condition from Langerhans cell histiocytosis and other illnesses related to dendritic cells. Within the existing categorization of histiocytic disorders, HLH is split into two main types: primary or familial HLH (FHLH) and secondary or reactive HLH (ReHLH) [16].

It might be challenging to differentiate between the two. Familial HLH is a group of uncommon immunological disorders that are inherited in an autosomal recessive manner. These disorders are caused by genetic flaws in different genes that all impact the cytolytic pathway. The clinical signs typically manifest within the initial two months of life [17]. Similar to MAS, the clinical progression of HLH is marked by a continuous fever and enlargement of the liver and spleen. Neurological symptoms have the potential to complicate and often take precedence in the clinical course. Less frequent occurrences of hemorrhagic rash and lymphadenopathy are seen. The laboratory results show a combination of low blood cell counts (especially low platelet count), increased liver enzymes, high levels of triglycerides, high levels of ferritin, and low levels of fibrinogen. These findings are similarly similar to those seen in macrophage activation syndrome (MAS). Similar to MAS, the presence of hemophagocytosis in the bone marrow is a characteristic feature of HLH [18].

Macrophage Activation Syndrome (MAS) is a rather common consequence of pSLE and is characterized by numerous diagnostic difficulties, which may result in a delayed diagnosis and/or an underestimation of this complication. The presence of a persistent and/or septic-like fever, along with other clinical manifestations such as hepatosplenomegaly and lymphadenopathy, may indicate the diagnosis of MAS. However, the occurrence of MAS before a diagnosis of pSLE has been made can make it difficult to recognize the condition in a timely manner [19]. Indeed, MAS frequently occurs at the beginning of pediatric systemic lupus erythematosus (pSLE). It is crucial to take into account particular criteria while diagnosing MAS in distinct rheumatic contexts. In relation to pSLE, the initial criteria established for patients already diagnosed with pSLE appear to be more effective than the ACR/EULAR criteria for sJIA-related cases (due to a lower ferritin threshold). This holds true even for patients who are diagnosed with pSLE after experiencing an episode of MAS as the first symptom of this rheumatic disease [20].

Macrophage Activation Syndrome (MAS) is a severe complication of rheumatic diseases like juvenile systemic lupus erythematosus (jSLE), characterized by excessive immune activation. While the literature does not specifically address the association of MAS with extremely elevated D-dimer levels in jSLE, D-dimer is a fibrin degradation product, and its elevation is generally associated with conditions involving thrombosis and fibrinolysis, which could be secondary to the hyperinflammatory state in MAS. The hyperferritinemia and hyperinflammation seen in MAS could theoretically contribute to a prothrombotic state, potentially leading to elevated D-dimer levels. However, this connection is not explicit [21,22].

Elevated D-dimer levels are often associated with various thrombotic and fibrinolytic disorders. In the context of macrophage activation syndrome (MAS), which is a severe hyperinflammatory condition, elevated D-dimer levels may be indicative of secondary coagulopathy due to increased fibrinolysis. This is consistent with the systemic activation of the coagulation cascade that can occur during MAS [23,24]. Interestingly, while elevated D-dimer levels are a common finding in MAS, the literature does not uniformly address this parameter across all studies. This omission suggests that while D-dimer is a relevant marker, it may not be

the primary focus in all MAS-related studies or may not be differentially elevated in MAS compared to other forms of HLH. Elevated D-dimer levels in MAS likely reflect the hypercoagulable state and secondary coagulopathy that can accompany the cytokine storm and systemic inflammation characteristic of this syndrome [25-27].

CONCLUSION

In conclusion, although MAS is a known complication of jSLE, its presentation as an initial symptom is rare. Extremely elevated D-dimer levels may indicate MAS, but this finding is uncommon in existing literature. Clinicians should maintain high vigilance for MAS in jSLE cases presenting with fever, cytopenias, and liver dysfunction, considering early intensive therapy for better outcomes. Further research is essential to clarify the pathogenesis and clinical significance 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.

AUTHOR'S CONTRIBUTIONS

Conceptualization, ZH and MM; methodology, ZH; validation, ZZ, MM, AE; formal analysis, ZZ, ME; 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.

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FIGURES

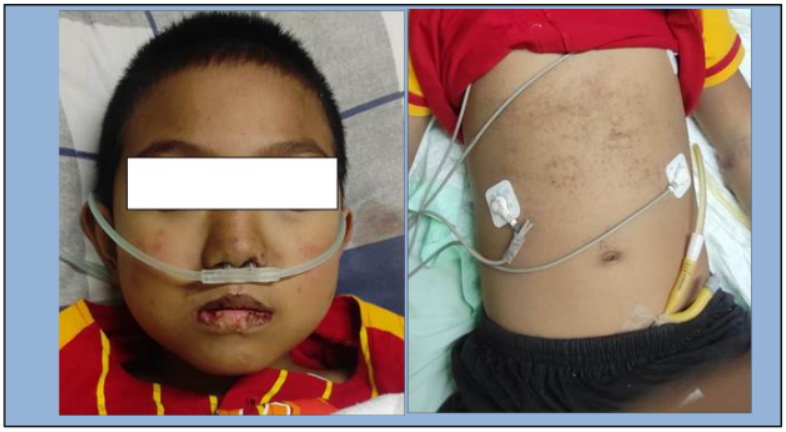

Figure 1. Rashes in face and trunk

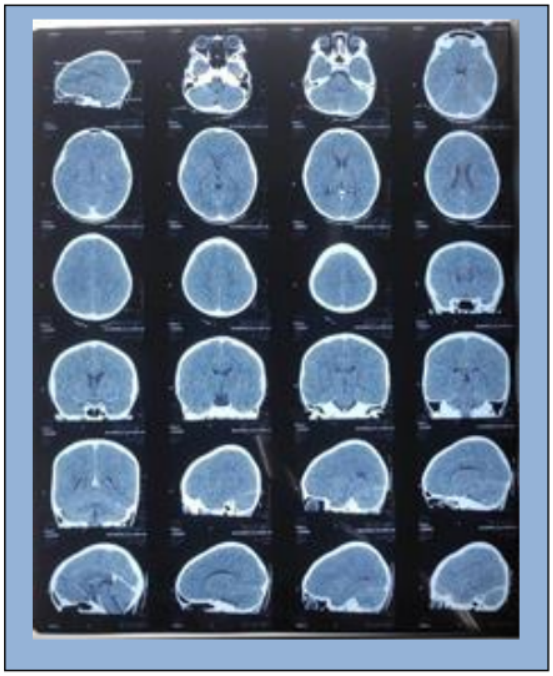

Figure 2. . Head CT Scan