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Macrophage Activation Syndrome as the Primary Presentation of Pediatric Systemic Lupus Erythematosus: A Case Report and Review of the Literature

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Abstract

Macrophage activation syndrome (MAS), in its secondary form, often complicates rheumatic diseases but rarely constitutes a mode of revelation. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology that primarily affects women in adulthood. MAS is a serious condition that may be the first presentation of SLE. Here, we report the case of a 4-year-old female with MAS as the primary manifestation of Systemic Lupus Erythematosus (SLE). In this case, we outline the characteristics of a complex case of SLE that was initially accompanied with MAS, and also review the literature to discuss the clinical, biological, and therapeutic aspects of this condition.

Keywords

Macrophage Activation Syndrome, Systemic Lupus Erythematosus, Child

1. Introduction

Macrophage activation syndrome (MAS) presents itself as a potentially life-threatening complication of rheumatic diseases such as systemic juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE). It is frequently considered a type of secondary hemophagocytic lymphohistiocytosis (HLH). SLE is an autoimmune inflammatory disease that impacts various organ systems and leads to considerable morbidity and mortality. Pediatric SLE accounts for approximately 10% to 20% of all SLE patients [1]. The severity of this condition

surpasses that observed in adults due to its aggressive clinical presentation and course, such as severe renal damage [2]. It is rare in children, especially before the age of 5 [3], but often severe, and mainly affects girls of peri-pubertal age.

Hematologic complications are a common issue in SLE and include leukopenia, lymphopenia, thrombocytopenia, autoimmune hemolytic anemia, antiphospholipid syndrome (APS), and thrombotic thrombocytopenic purpura and macrophage activation syndrome (MAS) [3].

Macrophage activation syndrome (MAS) is characterized by excessive activation of macrophages and lymphocytes, resulting to multiorgan dysfunction. As the initial manifestation of systemic lupus erythematosus (SLE), MAS is rare in children [4].

We report the case of a 4-year-old girl in whom the diagnosis of lupus erythematosus and macrophage activation syndrome was simultaneously made with response to the use of corticosteroids and hydroxychloroquine. This case highlights the features of this rare condition and discusses the clinical, diagnostic and pathogenetic particularities.

2. Clinical Observation

We present the case of a previously healthy 4-year-old child female, from a non-consanguineous marriage. She was referred to our department for the management of a generalized tonico-clonic convulsion, with a history of persistent fever lasting 12 days, with a maximum body temperature at 39˚C. The fever was accompanied by generalized fatigue. The patient was treated intermittently with antipyretics; however, the symptoms persisted. The evolution was marked by the appearance of a generalized tonic-clonic convulsion.

She did not have any prior infections or immunodeficiencies. There was no presence of recent records indicating the occurrence of a COVID-19 infection. Additionally, there was an absence of details regarding past travel history or family history of rheumatic or autoimmune disease.

On admission, clinical examination revealed unconscious child with Glasgow coma scale score at 14/15. High-grade fever (41˚C), tachycardia (115 bpm) and the blood pressure was 89/61 mmHg. The skin examination indicated diffuse purpuric lesions. The patient had a hepatomegaly with a normal cardiopulmonary auscultation. The rest of clinical examination was without abnormalities.

In order to rule out the presence of autoimmune, infectious, or neoplastic disease. Repeated blood and urine cultures and a Viral screening tests for coronavirus disease (COVID-19), Epstein Barr virus (EBV), hepatitis B and C and human immunodeficiency virus (HIV), were unremarkable. The tuberculin sensitivity test was negative.

Laboratory routine showed bicytopenia (normocytic normochromic anemia (9 g/dL), thrombocytopenia (26 × 10^9/L), hyperleukocytosis (20.7 G/L), neutrophilia (17.23 G/L), aspartate transaminase (AST) at 158 U/L and alanine transaminase (ALT) at 69 U/L, hypoalbuminemia (27 g/dl), hypertriglyceridemia (400

mg/dL), hyperferritinemia (>2000 ng/mL) hypofibrinogenemia at 0.8 with a CRP at 210 mg/l, a ESR at 33 mm. Lumbar puncture was normal. An MRI of the brain was performed in order to investigate potential abnormalities associated with meningoencephalitis; however, it was subsequently sent back without any detectable anomalies. The patient was initially treated with three boluses of corticosteroid, acyclovir, and antibiotics based on C3G (ceftriaxone).

In addition, a myelogram showed with evidence of hemophagocytosis (**Figure 1**), direct and indirect Coombs' tests were positive.

Prolonged fever, hepatomegaly, bicytopenia, Hypofibrinogenemia, hyperferritinemia, Hypertriglyceridemia and image of hemophagocytosis were consistent with macrophage activation syndrome (MAS) according to 2016 MAS classification criteria.

Immunological screening indicated positive anti-DNA antibodies and antinuclear antibodies (ANA). IgM antibodies against cardiolipin were positive. Anti-beta2 glycoprotein1 IgM was positive, rheumatoid factor dosage was normal, Serum C3 and C4 complement factors were low.

A diagnosis of SLE was established according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria.

Abdominal ultrasonography revealed hepatomegaly (14.6 cm) (**Figure 2**) and no abnormality detected on echocardiography.

Intravenous methylprednisolone (500 mg once daily for three days) was the first line of treatment. Subsequently, from the next day of this high-dose steroid, ferritin and CRP levels trended down, and cytopenia started to improve, along with the resolution of fever. As for specific treatment, a broad spectrum sunscreen lotion, emollients along with oral corticosteroid (prednisolone) 2 mg/kg/d, hydroxychloroquine (6.5 mg/kg/d) and vitamin D supplements were further added to the patient.

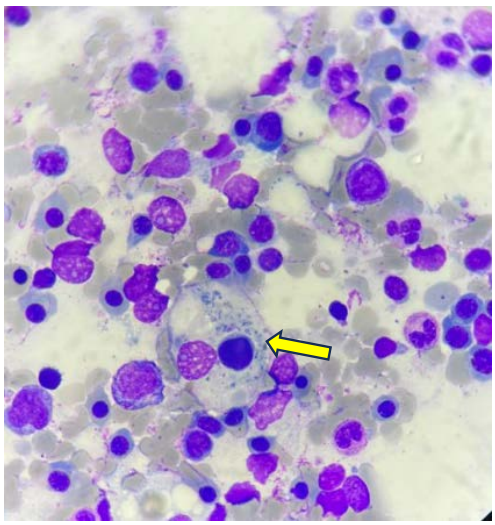

Figure 1. Images hemophagocytosis cells in a 4-year-old female with macrophage activation syndrome and systemic lupus erythematosus.

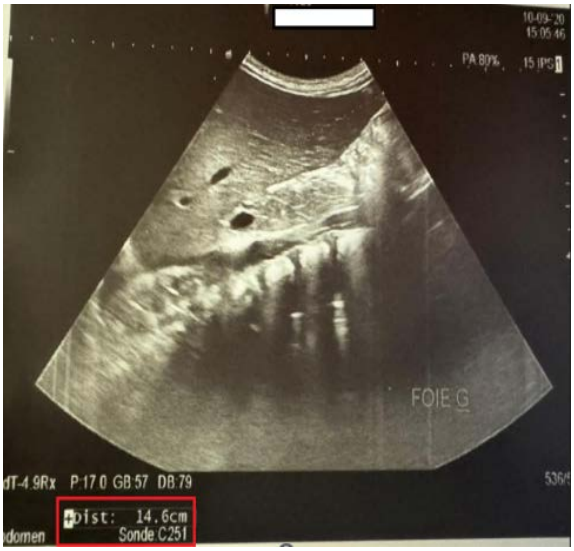

Figure 2. Abdominal ultrasonography revealed hepatomegaly (14.6 cm).

At the last follow-up, two years after starting treatment, the patient was doing well without any recurrences, the laboratory parameters returned to normal levels.

3. Discussion

Systemic lupus erythematosus (SLE) is a common autoimmune disease that presents before the age of 16 in 10% to 20% of cases, Systemic lupus erythematosus (SLE) represents a complex autoimmune disorder, which presents with a broad range of clinical manifestations. It is important to note that virtually all organ systems have the potential to be impacted by this condition. [5]. The SLE incidence varies from 1 to 10 per 100,000 person-year, and the prevalence is reported to range from 20 to 70 per 100,000 persons. Importantly, SLE is characterized by a clear gender predilection (female/male ratio up to 9:1), which is more pronounced than in other autoimmune diseases. [5] The prevalence of SLE in children is 6.3 per 100,000 (95% CI 5.7 - 7.0), a difference between women and men is observed (11.2 versus 1.8 per 100,000, respectively) [6].

MAS is an exceedingly grave, acute, and potentially life-threatening condition, which is categorized as a secondary form of hemophagocytic lymphohistiocytosis (HLH). Primary HLH is predominantly induced by genetic defects, resulting in the impairment of the T and/or NK cells cytotoxic activity. This immunological aspect is also the main pathogenic event of secondary or acquired HLH, namely MAS. The pathophysiology of MAS is still not fully understood. MAS may be due to a variety of factors, including the iatrogenic immunosuppression and/or intrinsic immune dysfunction related to the underlying rheumatic disease itself. Whenever one or more infectious agents (often viruses) cannot be efficiently cleared in rheumatic patients, the persistent activation of the CD8+ T cell/macrophage immune loop can result in uncontrolled systemic inflammation

and, thus, massive production of several inflammatory cytokines ("cytokine storm"), particularly TNF-α, M-CSF receptors, interleukin- (IL-) 1, IL-6, and interferon gamma- (IFN-) γ leading to dysregulated hemophagocytosis in multiple organs [7].

MAS is a serious complication of rheumatic diseases, with high reported mortality rates (8% - 22%) [5]. The SAM incidence associated with systemic juvenile idiopathic arthritis (JIA) is between 7% and 13% [8]. In contrast, SAM associated with lupus erythematosus (SLE) is rare, with an incidence of approximately 0.9% - 4.6% [9]. Furthermore, distinguishing between a flare-up of rheumatic disease and SAM can sometimes pose challenges. [10]. In certain scenarios, SAM associated with SLE may not be recognized due to similar biological characteristics with the disease itself. Morales *et al.* [11] evaluated bone marrow samples from 28 SLE patients. They found that 73.3% had hemophagocytosis, which did not correlate with SLE severity, serum complement, or anti-DNA antibody titers [11].

Regardless of the specific clinical history, the initial identification of MAS was initially established upon the same set of diagnostic standards employed for primary HLH (HLH-2004 classification system), which include clinical, laboratory and histopathologic findings (fever, splenomegaly, cytopenia, elevated triglycerides/decreased fibrinogen, decreased NK cell function, increased ferritin, and increased soluble IL-2 receptor levels, demonstration of hemophagocytosis) [5].

The identification of early MAS frequently poses a considerable challenge due to the lack of any distinct clinical characteristic or laboratory examination that definitively indicates its presence. According to a consensus conference of international experts on MAS, a febrile patient is classified as having MAS if the patient has ferritin > 684 ng/ml and at least two of the following four laboratory abnormalities: platelets < 181 × 10^9/L, AST > 48 U/L, triglycerides > 156 mg/dl, and fibrinogen < 360 mg/dl [6].

In 2009, Parodi *et al.* described 38 patients with ascertained diagnosis of pediatric SLE (pSLE), who eventually developed MAS. Borgia *et al.* described 38 pSLE patients with MAS (representing 9% of a cohort of 403 children affected with SLE). First, 68% of these patients had a concomitant diagnosis of MAS and pSLE, indicating that a previous diagnosis of pSLE was present in 32% of cases only, which is consistent with our case report [5].

The diagnosis of (MAS) in patients with (SLE) is regarded as a challenging task owing to the presence of comparable clinical manifestations, consequently resulting in the underdiagnosis of MAS in these particular patients. Delayed diagnosis of MAS is linked with increased morbidity and mortality due to different therapeutic methods [6].

Additionally, MAS is rare as initial presentation of SLE. Presence of fever, hyperferritinemia, cytopenia and liver dysfunction needs to increase the suspicion of MAS in SLE patients. Neurological manifestations were found to be more common in SLE patients with MAS than those without [6].

Children with MAS and a known rheumatic disease may receive varying treatments, including high-dose methylprednisolone, cyclosporine, cyclophosphamide, mycophenolate mofetil (MMF), azathioprine, rituximab, or interleukin-1 (IL-1) antagonists (7,9). These immunosuppressive medications are commonly selected due to their dual efficacy against the underlying rheumatic disease and MAS. IVIg is not effective as a monotherapy and typically used in combination with other medications [4].

4. Conclusion

In conclusion, MAS-associated SLE is rare. The MAS is one of the rare hematologic manifestations of SLE which is typically undervalued and presents a diagnostic challenge. Early detection and prompt treatment have the potential to reduce morbidity among these patients.

Consent

Written informed consent was obtained from the patient parents for publication of this case report and accompanying images.

Author Contributions

All authors contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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