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MACROPHAGE ACTIVATION SYNDROME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOUS TRIGGERED BY TUBERCULOUS MENINGITIS

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH), is characterized by systemic uncontrolled inflammation resulting from immune dysregulation secondary to various triggers, including genetics, infections, autoimmune diseases, and malignancies. Macrophage activation syndrome (MAS) is an immune dysregulation phenomenon, in which an underlying rheumatological disease is present. We report a rare, interesting case of a middle-aged female, with a systemic lupus erythematosus (SLE) flare complicated by macrophage activation syndrome (MAS), in which tuberculous meningitis (TBM) was the identified trigger.

Case report: A 48-year-old female with an African ethnic background, diagnosed with SLE, presented with a 2-week history of high-grade fever, cough, and worsening arthralgia. She was initially admitted with suspected SLE flare secondary to community acquired pneumonia and was started on broad-spectrum antibiotics. Later during her hospital stay, she underwent extensive workup because of her clinical condition, as she had continuous spikes of fever, progressive cytopenia, accompanied with acute confusion state despite treatment. She was ultimately diagnosed with SLE flare complicated by MAS secondary to TBM in view of persistent fever, neuropsychiatric symptoms, hyperferritinemia and hypertriglyceridemia, supported by bone marrow aspiration findings, a tuberculosis (TB) positive contact and supporting cerebrospinal fluid analysis suggestive of TBM. She was immediately started on pulse doses of steroids and anti-tuberculosis medications in which significant clinical improvement was observed. She was discharged home, with continuity of care done at the outpatient department in addition to continuity of physical rehabilitation.

Conclusion: Given the wide range of clinical presentations and similarities between SLE and the life-threatening MAS, it is essential to maintain a high level of suspicion to establish the diagnosis and promptly start the necessary treatment to ensure better clinical and survival outcomes.

KEYWORDS

Hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), systemic lupus erythematosus (SLE), National Early Warning Score (NEWS)

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LEARNING POINTS

- The wide range of clinical presentation of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) makes it a challenging diagnosis. Hence, a high index of suspicion is necessary to establish the diagnosis and promptly start the necessary treatment.
- The mainstay of treatment is the early identification and management of the underlying etiology of MAS along with high-dose glucocorticoids and other immunosuppressive therapy targeting the immune dysregulation pathway.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic disease of an autoimmune origin presenting with various clinical features involving multi-organ systems[1,2]. The hypothesis behind its pathogenesis is based on the production of autoimmune antibodies that form immune complexes deposited in various organs causing chronic inflammation and subsequent damage[2]. Macrophage activation syndrome (MAS) is one of the rare presentations that can complicate SLE flares and can be fatal if not treated promptly. MAS is defined as a life-threatening hyperinflammatory syndrome characterized by excessive activation and proliferation of T-lymphocytes and macrophages and a consequent massive production of cytokines or "cytokine storm" over the background of an underlying autoimmune condition[2]. Acute lupus hemophagocytic syndrome (ALHS) is defined as reactive haemophagocytosis detected in patients with underlying poorly controlled or active SLE[3]. Multiple triggering factors can be contributing to the development of this immune dysregulation including genetics, infections, autoimmune diseases, and malignancies[4].

We report a rare, interesting case of a middle-aged female, with SLE flare complicated by MAS, in which tuberculous meningitis (TBM) was the identified trigger.

CASE DESCRIPTION

A 48-year-old female with an African ethnic background, a known case of SLE diagnosed around 12 months before presenting to our facility, not on active treatment due to financial, and psychosocial constraints, presented to a tertiary care hospital in Dubai with 2 weeks history of high-grade fever, cough, and worsening arthralgia. Upon assessment, she was found to have blood pressure of 117/74 mmHg, pulse rate of 102 beats per minute, respiratory rate of 30 breaths per minute, tympanic temperature of 39.1°C, otherwise maintaining saturation on room air. Her initial National Early Warning Score (NEWS) was 6. Physical examination revealed an underweight middle aged-female, severely malnourished, with prominent cheek bones and loss of facial fat pads. Bilateral hand examination revealed Jaccoud's type of arthropathy. Chest auscultation revealed bilateral basal crepitations. The rest of the physical examination was unremarkable.

Initial investigations revealed a white cell count of 4.6 ×10^3/µl (3.6-11×10^3/µl), haemoglobin of 7.7 g/dl (12-15 g/dl), platelets of 396 ×10^3/µl (150-410 ×10^3/µl), and moderately elevated markers of sepsis, C-reactive protein 43 mg/l (<5 mg/l) and procalcitonin of 0.08 ng/ml (<0.05 ng/ml). Renal and liver profiles were within normal values, except for hyponatremia 120 mmol/l (136-145 mmol/l) and hypoalbuminemia 2.9 g/dl (3.4- 4.8 g/dl). Further workup to confirm the diagnosis of SLE and to explore the ongoing activity index was done. SLE was confirmed by high level of rheumatoid factor 37.3 IU/ml (<14 IU/ml), positive antinuclear antibody (ANA) titre 1/320 homogenous and coarse speckled, high anti-double-stranded deoxyribonucleic acid (dsDNA) 201.27 IU/ml (≥ 100 IU/ml is positive), low complement C3 0.22 g/l (0.90-1.80 g/l) and C4 0.06 g/l (0.10-0.40), high extractable nuclear antigen (ENA) centromeres 6.197, and negative anti-cyclic citrullinated peptide (CCP) <8 U/ml (<17 U/ml). Chest X-ray revealed bilateral infiltrates.

The patient was admitted to high dependency ward in a

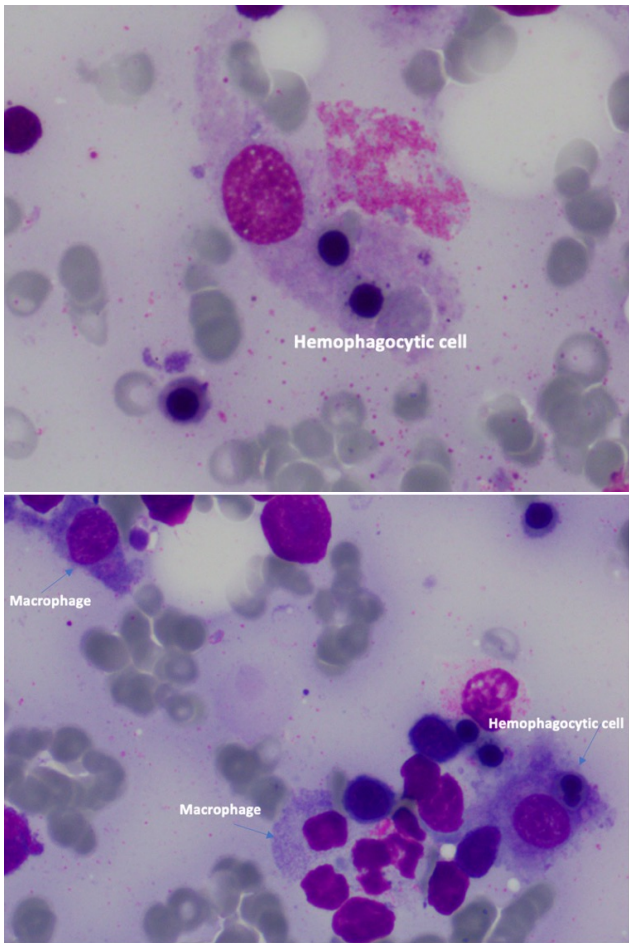


Figure 1. Bone marrow aspirate showing hemophagocytic cells along with an increased number of macrophages present.

monitored bed with the working diagnosis of SLE flare secondary to community acquired pneumonia, started on empirical intravenous antibiotics with coverage for possible atypical causative pathogens. Full sepsis workup was sent and was negative. Later during her hospital course, and despite all supportive measures and antibiotics, she continued to deteriorate, spiking high grade fever continuously, accompanied by new onset confusion and disorientation, with inability to recognize her close family members. Her vitals upon reassessment revealed blood pressure of 121/73 mmHg, pulse rate of 118 beats per minute, respiratory rate of 40 breaths per minute, oxygen saturation of 96% on 10 litres oxygen via non-rebreather mask, and tympanic temperature of 40°C. Her NEWS score doubled to 12. Due to the acute change in her mental status complicating her presenting complaints, she became confined to bed and fully dependent on nursing services. Following her rapid progression, further workup was carried out, including transthoracic echocardiogram and whole body computed tomography (CT) scan, which revealed no conclusive results. Repeated labs revealed bicytopenia, abnormal transaminases, very high ferritin and triglyceride levels, high D-dimer, and low fibrinogen, collectively raising the suspicion of acute lupus hemophagocytic syndrome (ALHS), which was later confirmed by the result of bone marrow aspiration *(Fig. 1)*.

A diagnosis is consistent with HLH if:
1. At least 3 of the following:
Fever
Splenomegaly
Cytopenia
Haemoglobin <9 g/l
Platelets <100 b/l
Absolute neutrophil count <1000 b/l
Hepatitis
2. At least 1 of the following:
Ferritin elevation >500 ng/ml
Elevated soluble CD25 (soluble IL-2-receptor)
Haemophagocytosis seen on tissue biopsy
Low/absent NK-cell activity
3. Other supportive features (not required):
Hypertriglyceridemia (fasting, >265 mg/dl)
Hypofibrinogenemia (<150 mg/dl)
Hyponatremia

Table 1. Commonly used diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), adapted from Henter et al[7].

Lumbar puncture was also done as part of the evaluation for her new onset confusion and showed features consistent with bacterial versus tuberculous meningitis in view of low glucose and high proteins in cerebrospinal fluid (CSF) analysis. The suspicion of TBM was high especially in view of her ethnic background in which TB is endemic, along with positive history of living in a household with close contact to a confirmed TB case, and indeterminate results of the QuantiFERON TB-gold test (interferon gamma-release assay, IGRA) done twice.

The patient was diagnosed with ALHS triggered by TBM as a complication of her presenting SLE flare. She was then started on pulse-dosing of methylprednisolone 500 mg intravenously, once daily for 3 days, followed by oral prednisolone 1 mg/kg per day, then tapered a month later based on her clinical response. She was also started on hydroxychloroquine 5 mg/kg per day, and cyclosporin 50 mg per oral twice daily as disease modifying anti-rheumatic therapies to control her underlying SLE. In addition, anti-TB medications were started, after consultation with an infectious disease consultant, which collectively reflected positively on her clinical condition causing significant improvement. She became afebrile and her vitals became stable. Her mental status returned to baseline: fully alert and oriented. She was able to get out of bed and preform daily activities independently until being discharged from the unit. Six weeks after discharge on her follow-up visit to the Rheumatology outpatient services, she had adequate clinical response with minimal required physical rehabilitation. It was further planned to continue tapering prednisolone, and to continue immunosuppressive therapy with anti-TB treatment for total duration of 12 months.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a broad term describing the immune dysregulation that occurs due to wide variety of stimuli[5]. However, MAS is termed when there is an underlying rheumatological condition. It is considered as an aggressive and life-threatening syndrome of excessive immune activation caused by the absence of normal downregulation of the immune system by activated macrophages and lymphocytes[5,6]. Haemophagocytosis is characterized by the engulfment of blood cells: red blood cells, platelets, and white blood cells within the cytoplasm of macrophages. It can be triggered by various underlying conditions: such as genetic mutations, malignancies such as lymphoma and leukaemia, rheumatological diseases such as juvenile arthritis and SLE, and finally infectious aetiologies[6]. The latter, specifically viral causative pathogens are considered the most common triggering factor behind HLH/MAS. Others include TB, fungal and parasitic infections[5]. The multisystem involvement contributing to the clinical presentation of HLH/MAS makes it a challenging diagnosis for physicians, with a wide scope of possible differential

diagnosis. HLH is more common in the paediatric age group, diagnosed based on the traditional HLH-2004 diagnostic criteria. A newer, modified version of this criteria that was established in 2009 "Modified 2009 HLH Criteria" can be used for all age groups as shown in *Table 1*[5,7].

According to the above reference, our case presented with prolonged fever, bicytopenia, elevated transaminases, markedly elevated ferritin, and hyponatremia meeting the criteria for HLH. Bone marrow biopsy showed the presence of hemophagocyte, which additionally supported the diagnosis of MAS complicating the case with the background of underlying SLE. The diagnosis of TBM was made after thorough discussion with our colleagues from the infectious disease unit considering the patient's background information and history of close contact with TB in addition to supportive CSF analysis results. Thus, it was the triggering factor that led to the development of MAS in our patient[8]. In a patient with an underlying poorly controlled rheumatological disease, namely SLE, who presents with a flare of autoimmune disease and does not show expected clinical improvement during her hospital stay, with failure of broad-spectrum antibiotics coverage and unconclusive results after undergoing extensive workup, the suspicion of MAS should be raised and taken into serious consideration prompting urgent treatment to ensure a better outcome. The mainstay of treatment is the early identification and management of the underlying aetiology of MAS along with high-dose glucocorticoids and other immunosuppressive therapy targeting the immune dysregulation pathway[9,10].

CONCLUSION

This case is challenging and interesting at the same time. Given the wide range of clinical presentations and similarities between SLE and MAS, it is essential to maintain a high level of suspicion to establish the diagnosis and promptly start the necessary treatment. Raising the suspicion of MAS should be considered in clinical contexts where there is a poorly controlled underlying rheumatological disease, especially in individuals where an unexpected response to conventical treatment modalities and further deterioration is noted.

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