Macrophage activation syndrome in a young adult patient with a background of systemic lupus erythematosus: a case report

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ABSTRACT

Background: Macrophage activation syndrome (MAS) is a rare but potentially life-threatening condition associated with systemic lupus erythematosus (SLE), as well as several other autoimmune conditions.

Case Presentation: We present a case of MAS in a 30-year-old patient with a background of SLE presenting with persistent fever and hemodynamic instability. Broad-spectrum antibiotics were initially started for possible sepsis of unknown origin, but a lack of response or evidence of an infection source led to further laboratory investigations and additional diagnostic imaging. Hyperferritinemia, a low fibrinogen, hypertriglyceridemia, and pancytopenia raised the suspicion of MAS. Echocardiography revealed a pericardial effusion requiring pericardiocentesis. With rapid disease progression, multiorgan failure ensued, and shortly after a high dose, methylprednisolone was commenced; the patient's condition worsened and she died after a cardiac arrest.

Conclusion: This case highlights the challenges involved in diagnosing MAS and in differentiating it from more common presentations such as sepsis or autoimmune disease flares, and demonstrates the possible rapid disease progression. Therefore, early recognition of certain clinical features and laboratory markers are essential to enable early diagnosis, commencement of immunosuppressive treatment, and to ultimately improve outcomes in such critically unwell patients.

Keywords: Macrophage activation syndrome, systemic lupus erythematosus, rare rheumatology diseases, diagnosis, ferritin, mortality, abstract.

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Background

Macrophage activation syndrome (MAS) was first recognized as a severe complication in young patients with systemic juvenile idiopathic arthritis (SJIA) in the 1980s. It is categorized as a subset of secondary hemophagocytic lymphohistiocytosis (HLH). MAS is associated with other rheumatological conditions such as systemic lupus erythematosus (SLE) and adult-onset Still's disease (AOSD) [1]. The prevalence of MAS in patients with SLE is low (0.9%-4.6%) [2], but the high mortality associated with MAS (5%-35%) [3-5] makes early recognition and commencement of treatment essential to improve survival.

MAS is predominantly characterized by excessive proliferation of macrophages and cytotoxic T-lymphocytes, causing cytokine overproduction, including macrophage colony-stimulating factor, interferon gamma, tumor necrosis factor alpha, and interleukins (IL) 1, 2, 8, and 16 [1]. The resulting inflammatory process signals a gamut of clinical signs and symptoms including persistent fever, hepatomegaly, splenomegaly, lymphadenopathy, hemorrhagic manifestations (nosebleeds, bruising, and petechiae), and neurological dysfunction (headaches, confusion, seizures, and coma) [1]. Fever is almost always present, and one MAS study (N = 95) noted fevers in 98.9% of the patients [6]. Patients with MAS can deteriorate rapidly, leading to multiorgan failure and death.

Laboratory investigations play a key role in the diagnosis of MAS. Although there are no specific diagnostic criteria for MAS associated with SLE, the 2016 classification criteria for MAS complicating SJIA includes a raised ferritin (>684 ng/ml) *and* any two of the following: low platelets (PLT) (≤181 × 10^9/l), low fibrinogen (≤360 mg/dl), raised aspartate aminotransferase (AST) (>48 U/l), and raised triglycerides (>156 mg/dl) [6]. Other common laboratory findings include *raised* alanine aminotransferase (ALT), lactate dehydrogenase (LDH), D-dimer, procalcitonin (PCT), and c-reactive protein (CRP), as well as *reduced* white cell counts (WCC), neutrophils, fibrinogen, erythrocyte sedimentation rate (ESR) (relative to CRP), albumin, hemoglobin (Hb), and sodium (Na). Fardet et al's [7] validated H-score is another useful

tool for helping to determine the probability of secondary HLH. Histological analysis of bone marrow aspirates may help in MAS. To illustrate this, a multicenter study involving 362 patients with MAS who underwent bone marrow aspirate analysis found hemophagocytes in around 60% of the patients [8]. However, this is not pathognomonic.

The following case is unique in that it provides an account of a previously quiescent SLE disease manifesting with MAS. The authors hope to illustrate the importance of considering a diagnosis of MAS in a rapidly deteriorating patient who is not responding to treatment for unproven sepsis. The relatively low ESR is an early ominous sign and a useful pattern to recognize. Other important laboratory signs of significance in MAS is hyponatremia, particularly with cerebral agitation.

Case Presentation

A 30-year-old female patient presented to the emergency department with a 4-day history of myalgia, arthralgia, and fever having undergone abdominal incisional hernia repair surgery 2 weeks prior. She had a background of mild and stable SLE (diagnosed 3 years prior) which was well managed without disease modifying medications.

Observations: fever (T = 39.6°C), hypotension (BP = 108/66 mmHg), and tachycardia (HR = 106/minute).

On examination, cervical lymphadenopathy was present. The surgical wound site was clean, and no hepatomegaly or splenomegaly or visible rashes were detected.

Previous laboratory results, sourced from prior rheumatology clinic letters, revealed antinuclear antibody (ANA) 1:640 speckled pattern, Ro +, La +, equivocal/mildly elevated double-stranded DNA (dsDNA) antibodies, negative antiphospholipid, and anti-neutrophil cytoplasm antibodies.

With the background diagnosis of SLE, the rheumatologists felt that the fever, lymphocytopenia, and neutropenia could suggest active SLE. Therefore, early in the course of her hospitalization, prior to immunology result availability, she was started on 30 mg prednisolone/day, but the overall priority was given to possible sepsis.

The day following hospital admission, she was moved to the intensive care unit due to persistently low blood pressure, requiring vasopressors despite aggressive fluid resuscitation. The next day, she became severely agitated, confused, and aggressive and required sedation, intubation, and ventilation.

Her oral prednisolone treatment was converted to 50 mg intravenous (IV) hydrocortisone four times daily (QDS). She also received 3 doses of 100 ml 20% human albumin solution and continued with broad-spectrum antibiotics (Meropenem) and vasopressors.

The patients laboratory results are presented in Table 1, with a neutropenia, lymphocytopenia, thrombocytopenia,

Table 1. *Laboratory investigations.*

LABORATORY INDEX	RESULT	NORMAL RANGE
WCC	1.9 × 10^9/l	3.8-11.1 × 10^9/l
Neutrophils	1.5 × 10^9/l	2-7.5 × 10^9/l
Lymphocytes	0.4 × 10^9/l	1.5-4 × 10^9/l
Hb	95 g/l	115-155 g/l
PLT	40 × 10^9/l	150-400 × 10^9/l
ALT	44 iμ/l	0-33 iμ/l
Triglycerides	11.94 mmol/l	<2.3 mmol/l
Fibrinogen	1.09 g/l	1.5-4 g/l
Ferritin	29,767 μg/l	30-400 μg/l
LDH	1,681 iμ/l	0-250 iμ/l
Procalcitonin (PCT)	>100 ng/ml	0-0.06 ng/ml
ANA	Positive	N/A
Double-stranded DNA (dsDNA)	4.7 IU/ml	<10 IU/ml
C3	0.87 g/l	0.75-1.65 g/l
C4	0.13 g/l	0.20-0.65 g/l
ESR	17 mm/hour	<15 mm/hour
CRP	344 mg/l	0-5 mg/l
Anticardiolipin IgG	2.3 U/ml	Weak positive: 15-40 U/ml Positive: >40 U/ml
Anticardiolipin IgM	3.7 U/ml	Weak positive: 15-40 U/ml Positive: >40 U/ml
Hepatitis B	Negative	
Hepatitis C	Negative	
HIV	Negative	
Blood cultures × 3	Negative for bacterial growth	
Urine dipstick	Proteinuria 2 + Erythrocyturia 3 +	
Urine M, C, S	Negative for growth	
Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) swab polymerase chain reaction (PCR)	Negative	

Table 2. *Imaging on admission.*

IMAGING	RESULT
Chest X-Ray	Normal
Computed tomography (CT) abdomen and pelvis with contrast	Reactive pelvic lymphadenopathy but with no other significant findings
Echocardiogram (bedside)	Good left ventricular function and no effusions

Table 3. *Imaging on day 3.*

IMAGING	RESULT
CT Brain	Normal
CT abdomen and pelvis with contrast	New bilateral pleural effusions, new intra/extra-peritoneal fluid collection in the pelvis, in addition to the pre-existing pelvic lymphadenopathy

Table 4. *Summary of the disease course.*

DAY	COURSE	THERAPY
1	Presentation and initiation of broad-spectrum antibiotics for presumed sepsis	Broad-spectrum antibiotics (Meropenem) and 30 mg oral prednisolone
2	Admission to HDU for vasopressor support	Continued IV antibiotics and IV hydrocortisone
3	Agitation requiring sedation, intubation, and ventilation	Continued IV antibiotics and 200 mg IV hydrocortisone
4	Worsening multiorgan failure	RRT, 200 mg IV hydrocortisone
5	Diagnosis of MAS likely secondary to SLE based on laboratory findings correlated with scoring systems and deterioration with no proven infection	High dose IV methylprednisolone pulse
6	Pericardiocentesis, cardiac arrest, and death	

mildly deranged liver enzymes, triglyceridemia, hyperferritinaemia, hypocomplementemia (low C4), raised CRP and positive ANA with no dsDNA antibodies. Table 2 summarizes the initial imaging and Table 3 the results of a repeat CT showing new serositis.

The diagnoses of HLH and MAS, secondary to SLE, were considered. The fever, pancytopenia, hyponatremia, pleural effusions, and absence of a definite infection source were the main supporting points raised by the rheumatologists. The patient scored high on the scoring systems for both HLH and MAS [6,7]; but as her SLE had previously been described as very mild and the intensivists were not convinced that adequate time had been allowed to rule out covert sepsis, it was agreed to monitor the patient closely on continued antibiotics for another 12 hours before commencing pulsed intravenous methylprednisolone.

Unfortunately, during the night this patient progressed to multiorgan failure. Renal replacement therapy (RRT) was started for progressive metabolic acidosis and worsening renal function. A repeat of the echocardiogram revealed a pericardial effusion, necessitating an emergency pericardiocentesis, which drained approximately 200 ml of serous fluid. Following this, she received a pulsed dose of 1 g of IV methylprednisolone. Despite the aggressive management as per above, the patient continued to deteriorate and sustained a cardiac arrest and died 24 hours later. Table 4 summarises the disease course.

Discussion

This case demonstrates the rapid disease progression in patients with MAS, stressing the importance of early diagnosis and treatment. However, diagnosing MAS is challenging as it presents similarly to other more common conditions, such as sepsis and SLE flare-ups. Although we focus on MAS, it is useful to consider both MAS and secondary - HLH (sHLH) as cytokine storm syndromes, where fulminant sustained hypercytokinemia is the common factor. These often relate to underlying autoimmune /autoinflammatory conditions or infections (commonly Epstein-Barr virus) [9]. Other triggers of sHLH are hematological malignancy and hematopoietic stem cell transplantation [10].

The authors would like to highlight the learning points in this case which help recognize MAS.

Beginning with the clinical presentation, neurological dysfunction (headaches, confusion, seizure, and coma) is an important clinical manifestation and may be present in ~43% of the patients with MAS [6]. As with this case, in the context of other clinical features and laboratory results, it should raise suspicions of MAS and prompt further investigation. The confusion and agitation seen in this case report were initially attributed to prednisolone side effects; however, in hindsight, this was more in keeping with a neurological manifestation of MAS.

Laboratory blood tests were generally helpful in giving us clues to possible MAS. Our laboratory findings correlated with Gavand et al.'s [3] study looking at over 100 episodes of MAS complicating SLE where hyperferritinaemia was seen in 96% of the cases, followed by raised levels of AST (94.7%), LDH (92.3%), CRP (84.5%), and PCT (83.6%). Therefore, a high ferritin, along with raised AST, LDH, CRP, and other clinical features, should raise suspicions of MAS. Ruscitti et al.'s [11]'s study, involving

41 cases of MAS complicating autoimmune disease, related increased serum ferritin levels with higher mortality demonstrating the added importance of ferritin levels as a prognostic marker in MAS [11]. Pancytopenia is another key laboratory pattern observed in MAS and is caused by the deposition of immune complexes onto hematopoietic stem cells, leading to their subsequent depletion.

Certain laboratory markers can also be misleading. For example, PCT, a peptide precursor of the hormone calcitonin, is often used to confirm the diagnosis of bacterial infections. However, this can, as one study found (N = 80), be raised in around 84% of the patients with MAS associated with SLE [3]. Our patient had a raised PCT level. CRP is likewise raised in both MAS and sepsis. An atypical laboratory pattern of a low ESR level relative to the CRP is seen is MAS. In this case, the ESR of 17 mm/hour was relatively low compared with the CRP level (344 mg/l). A low ESR is typically seen concomitantly with a low fibrinogen, and it is useful to recognize this pattern to help aid diagnosis and to differentiate MAS from conditions like active SLE flare-up or infection, where ESR is typically raised [12].

In terms of imaging, X-rays, CT, and echocardiograms are useful. Our patient developed polyserositis (pleural effusions, ascites, and pericardial effusion), a finding noted in other published cases [2,13,14]. As these cases demonstrate, potentially life-threatening cardiac and respiratory complications can develop rapidly and should, therefore, be considered and monitored throughout management in MAS patients.

Several treatments have been used for MAS, but validated protocols are lacking [9]. Corticosteroids are used as first-line therapy including high-dose methylprednisolone (30 mg/kg daily max 1 g for 1-3 days). If the patient responds well to initial therapy, the dose is normally reduced to 2-3mg/kg daily, followed by tapering doses of oral prednisolone [1]. To highlight the effectiveness of corticosteroids in MAS, one study involving 57 cases of MAS complicating SLE found that high-dose steroids induced remission in 65% of the cases [3].

In cytokine storm syndromes, IL-1 is a key factor in hyperinflammation [9]. Anakinra, a recombinant humanized IL-1 receptor antagonist, has gained much respect as a proposed key first-line therapy in critically unwell patients with a cytokine storm due to MAS/HLH [9]. In such patients, and in the presence of severe thrombocytopenia and neurological symptoms, intravenous administration (>2 mg/kg per day or >100 mg/day) delivers the higher doses required compared to subcutaneous (SC) injections, licensed for rheumatoid arthritis, systemic juvenile idiopathic arthritis, AOSD, and cryopyrin-associated periodic syndromes [9]. The authors would retrospectively recommend this in combination with dexamethasone and intravenous immunoglobulins as the most hopeful combination treatment, in this case, had it been given within the first 12 hours of suspicions of MAS. Dexamethasone (10 mg/m^2 IV daily) is preferred to methylprednisolone, where there is neurological involvement. There is yet to be formalized guidance and licensing of IV anakinra for these purposes stimulating UK initiatives to address this with a call for additional commissioning policies [9].

The other treatments, such as cyclosporin A, etoposide, cyclophosphamide, plasma exchange, anti-thymocyte globulin, canakinumab (β inhibitor), and tocilizumab (IL-6 inhibitors), can be considered as second-line agents in patients who do not respond well to steroids. Etoposide has been shown to be an effective treatment for MAS, and is recommended by the HLH 2004 protocol; however, it should be used with caution due to its potential side effects of severe bone marrow suppression, hepatotoxicity, and nephrotoxicity [15].

Conclusion

MAS is a rare but potentially life-threatening condition complicating SLE, with a high risk of mortality. Disease progression is rapid; therefore, early diagnosis and treatment are essential to improve outcome. MAS should be considered in patients with a background of autoimmune diseases presenting with fever. This is especially true when infection is unlikely or antimicrobial responses are poor. Raised levels of ferritin, AST, and triglycerides, as well as low PLT and low fibrinogen in combination with pancytopenia, are key diagnostic markers. PCT can be elevated in MAS. There is a need for validated protocols to treat the common pathway of cytokine storm and for commissioning policies to improve access to anakinra as a first-line agent.

What is new?

MAS is a rare complication of SLE; therefore, case reports discussing the presenting features, investigations, and diagnosis are limited. MAS is very difficult to diagnose, and delays lead to significantly increased mortality risk. This case offers key insights that will help clinicians recognize MAS as a differential diagnosis early on, so that the time taken to diagnose is shorter and patients can be started on treatment earlier (which is vital to improved outcome).

List of Abbreviations

AOSD	Adult onset stills disease
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AST	Aspartate aminotransferase
BP	Blood pressure
CRP	C reactive protein
CT	Computed tomography
dsDNA	Double stranded DNA
ESR	Erythrocyte sedimentation rate
Hb	Haemoglobin
HDU	High dependency unit
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis

HR	Heart rate
IL	Interleukin
IV	Intravenous
LDH	Lactate dehydrogenase
MAS	Macrophage activation syndrome
Na	Sodium
PCT	Procalcitonin
PLT	Platelet
QDS	Four times daily
Sars-Cov-2 PCR	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
PCR	Polymerase chain reaction
RRT	Renal replacement therapy
SJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
T	Temperature
WCC	White cell count

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Summary of the case

1	**Patient (gender, age)**	Female, 30-year-old
2	**Final diagnosis**	MAS based on the following 2016 criteria: raised ferritin (29,767 µg/l), low PLT (40 × 10^9/l), low fibrinogen (1.09 g/l), and raised triglycerides (11.94 mmol/l)
3	**Symptoms**	Fever, generalized muscle aches, and joint pain
4	**Medications**	Prednisolone and methylprednisolone
5	**Clinical procedure**	1 g IV methylprednisolone pulse therapy
6	**Specialty**	Rheumatology