CASE REPORT

A Case of COVID-19-Induced Macrophage Activation Syndrome in a Patient with Neuropsychiatric Lupus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with diverse clinical manifestations, and one of its rarer complications is the development of macrophage activation syndrome (MAS). This case report discusses the unique scenario of a 25-year-old female with a background of SLE who contracted COVID-19, triggering MAS and presenting with neuropsychiatric lupus. The patient exhibited symptoms including seizures, fever, altered consciousness, and neurological abnormalities. Laboratory investigations revealed pancytopenia, elevated inflammatory markers, and positive autoantibodies. Macrophage activation syndrome, characterized by inflammation, pancytopenia, and hepatosplenomegaly, can be a life-threatening complication of SLE. Its occurrence is often associated with infections or active SLE. This report highlights a unique trigger for MAS, the co-occurrence of COVID-19 in a patient with underlying SLE. Treatment included high-dose corticosteroids, immunosuppressive agents, and supportive care. The study emphasises the importance of early detection and the initiation of treatment. Prompt recognition of MAS, which can mimic sepsis or SLE flares, is crucial for effective management.
Malaysian Journal of Medicine and Health Sciences (2026) 22(SUPP5): 118-120. doi:10.47836/mjmhs.22.s5.22

Keywords: Systemic lupus erythematosus, macrophage activation syndrome, COVID-19, neuropsychiatric lupus, autoimmune disease.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the involvement of almost every organ of the body, a broad spectrum of clinical manifestations, and several immune-mediated abnormalities leading to multiple organ dysfunction. Among the wide range of clinical manifestations of SLE, the nervous system is also affected, leading to diverse central nervous system (CNS) and peripheral nervous system presentations (PNS). A manifestation of SLE known as neuropsychiatric SLE (NPSLE) is characterized by neurological and psychiatric symptoms. A severe complication of rheumatic diseases known as "macrophage activation syndrome" (MAS) is presently one of the secondary forms of hemophagocytic lymphohistiocytosis (HLH). Patients with SLE experience an incidence of MAS that is considerably lower than that of those with systemic juvenile idiopathic arthritis, ranging from 0.9 to 9% (1). Macrophage activation syndrome can also result from dysregulated and excessive immune responses, such as COVID-19 infection (2). Here is a case report of a young female diagnosed with COVID-19, in the background of SLE, triggering macrophage activation syndrome, with manifestations of neuropsychiatric lupus during her hospital stay.

CASE REPORT

A 25-year-old female presented to casualty with seizures, GTCS semiology, and COVID-19 infection. She had a low-grade intermittent fever and reduced verbal response for one month. On examination, she had a recorded axial temperature of 101 degrees Fahrenheit, and her other vitals were stable. The patient was pale and had bilateral oedema of the leg and ankle. On examination of CNS, her GCS was E1 V1 M4, Tone increased in all four limbs and power at least ⅗ in all four limbs, bilateral plantar was extensor, superficial reflexes normal, deep tendon reflexes of Ankle, knee and pectoral were exaggerated. In the hospital, she had an episode of seizure, GTCS semiology. Laboratory investigations are included in Table I.

Table I: Laboratory Investigations

Investigation	Result
HB	6.8 g/dl
Platelets	1.1 lakhs
Total counts	2820 cells/cumm(4000 to 11000)
ESR	10mm/hr
HRCT CHEST	NORMAL
COVID 19 RT-PCR	POSITIVE
ANA by IFA	3+ cytoplasmic Pattern positive Strong anti-Smith, anti-dsDNA, anti-U1 RNP, anti-Ro 52- anti-SSA.
serum LDH	314 U/L (120-246 U/L)
serum ferritin	3550 ng/ml (6.24 - 137 ng/ml for <50 y female)
serum fibrinogen	126 mg/dl (200-400 mg/dl)
DCT	positive
Triglycerides	359 mg/dl (< 150 mg/dl)
C3	75 mg/dl (80 -175 mg/dl)
C4	7 mg/dl (12-42 mg/dl)

Legend
HB: Hemoglobin concentration in grams per deciliter (g/dL)
Platelets: Platelet count in thousands per microliter (lakhs)
Total counts: Total white blood cell count in cells per cubic millimetre (cells/cumm)
ESR: Erythrocyte sedimentation rate in millimetres per hour (mm/hr)
HRCT CHEST: High-resolution computed tomography findings for the chest (NORMAL)
COVID 19 RT-PCR: COVID-19 Reverse Transcription Polymerase Chain Reaction (POSITIVE)
ANA by IFA: Antinuclear Antibodies by Indirect Immunofluorescence Assay (3+ cytoplasmic Pattern positive)
serum LDH: Serum lactate dehydrogenase levels in units per litre (U/L)
serum ferritin: Serum ferritin concentration in nanograms per milliliter (ng/ml)
serum fibrinogen: Serum fibrinogen concentration in milligrams per deciliter (mg/dl)
DCT: Direct Coombs Test (positive)
Triglycerides: Triglyceride levels in milligrams per deciliter (mg/dl)
C3: Complement component 3 levels in milligrams per deciliter (mg/dl)
C4: Complement component 4 levels in milligrams per deciliter (mg/dl)

CSF analysis was normal. MRI Brain revealed a normal study. A nerve conduction study showed severe axonal polyneuropathy of upper and lower limbs with sensory axonal Neuropathy of lower limbs. The patient was diagnosed with COVID-19 INFECTION-MACROPHAGE ACTIVATION SYNDROME-NEUROPSYCHIATRIC LUPUS. Because of pancytopenia & covid RT PCR positivity and given blood parameters (increased ferritin, increased triglyceride, decreased fibrinogen), macrophage activation syndrome, and high suspicion of an autoimmune disease (SLE)- she was put on pulse methylprednisolone 500 mg iv od for 3 days and then tapered down. Inj 20% Human albumin infusion iv over four hours for three days was given in view of hypoalbuminemia and volume overload status, two PRBC transfusions were done in view of low Hb, Steroid sparing agent T.cyclosporine 50mg BD and DMARD T.HCQ 200 mg OD were added subsequently while tapering steroids. Because of Neuropsychiatric manifestations after tapering steroids, the patient was put on a course of Rituximab. The patient showed improvement with disease activity under control, C3 and C4 levels improving, and continued on immunosuppression and low-dose steroids with regular follow-up.

DISCUSSION

A potentially fatal severe inflammatory condition known as macrophage activation syndrome (MAS) is characterized by pancytopenia, coagulopathy, hepatopathy, neurological problems, and hemophagocytosis. Unchecked macrophage and T cell activation is what causes the inflammation (3). High fever, secondary pancytopenia, signs of hepatosplenomegaly and hepatic dysfunction, lymphadenopathy, and hyperferritinemia are seen in the patients. The prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels are frequently abnormal. Haemorrhages or purpura may also be present. Headache, temporal-spatial disorientation, irritation, convulsions, or coma are examples of neurological symptoms (3). Cytokine storm, particularly MAS, is involved in coronavirus disease 2019 (COVID-19)-associated pneumonia and its exacerbation. Due to the extensive-expression of virus entry receptors, the start of the local inflammation brought on by SARS-CoV-2 infection activates macrophages at that spot. It quickly spreads to the entire lung, which later transforms into a systemic multiorgan failure (2). MAS is a potentially fatal complication of SLE. Its occurrence is most usually linked to an infection or current SLE disease. Patients with SLE who have unexplained fever, cytopenia, or liver dysfunction together with elevated ferritin and LDH levels should be suspected of having MAS (4).

The 25-year-old female patient presented with a unique and severe clinical scenario. The simultaneous presence of seizures, fever, altered consciousness, and neurological abnormalities complicated the diagnostic process. Laboratory findings such as pancytopenia, elevated inflammatory markers, and positive autoantibodies, alongside the clinical symptoms, pointed towards MAS triggered by COVID-19 in the background of SLE.

The presence of hemophagocytosis on a bone marrow biopsy is extremely suggestive but not necessary for the diagnosis. High-dose intravenous corticosteroids are the first-line treatment, along with the proper supportive care, and cyclosporin or intravenous immunoglobulin (IVIg) may be administered if the initial response is unsuccessful (5). In this patient, high-dose intravenous corticosteroids were administered as the first-line treatment, supplemented with supportive care, and cyclosporin. The use of pulse methylprednisolone and subsequent tapering, coupled with additional

immunosuppressive therapy (e.g., cyclosporine and HCQ), illustrates the multifaceted approach required for managing such cases. The inclusion of Rituximab was crucial due to the neuropsychiatric manifestations after tapering steroids. Etoposide and anakinra are other management options.

Early detection of MAS is essential to its treatment, although this can be challenging given that it resembles systemic sepsis or flares of the underlying rheumatic condition. Differentiating MAS from sepsis and SLE flares involves a combination of clinical assessment and specific laboratory markers. MAS is characterized by persistent high fever, pancytopenia, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. The presence of hemophagocytosis on bone marrow biopsy, although not necessary for diagnosis, strongly suggests MAS. Elevated ferritin levels (>500 ng/mL), especially when exceedingly high, are more indicative of MAS than sepsis or SLE flares.

In contrast, sepsis often presents with leukocytosis or leukopenia, elevated procalcitonin levels, and positive blood cultures, which are less commonly seen in MAS. SLE flares are typically associated with an increase in disease activity markers such as anti-dsDNA antibodies and hypocomplementemia (low C3 and C4 levels), which may also occur in MAS but are not exclusive to it. Furthermore, the rapid and marked response to high-dose corticosteroids and immunosuppressive therapy in MAS, as observed in this patient, helps distinguish it from sepsis, which requires antimicrobial therapy and source control, and from SLE flares, which may respond to steroids but lacks the same constellation of severe hematologic and biochemical abnormalities.

Such cases as reported above have broader clinical implications in medical practice. Routine screening for early signs of MAS in patients with SLE, particularly during infections, can facilitate timely intervention. This includes monitoring for symptoms like persistent fever, neurological abnormalities, and lab markers such as ferritin, triglycerides, and fibrinogen levels. Given the patient's neuropsychiatric manifestations, regular neurological evaluations and cognitive assessments should be integrated into the monitoring protocol. Managing MAS in SLE patients requires a multidisciplinary team involving rheumatologists, infectious disease specialists, hematologists, and neurologists to provide comprehensive care. Patients recovering from MAS should be monitored long-term for potential relapses and complications. Follow-up visits should include comprehensive evaluations of organ functions and immune status, as well as monitoring for disease activity in SLE using disease activity scoring systems and inflammatory markers like CRP, ESR, and complement levels (C3, C4).

CONCLUSION

This case report underscores the critical relevance of understanding the intricate interplay between systemic lupus erythematosus (SLE), COVID-19 infection, and the development of macrophage activation syndrome (MAS), particularly in the context of neuropsychiatric lupus manifestations. The discussion elucidates the diagnostic challenges posed by MAS, emphasizing the importance of a high index of suspicion in patients with SLE. Early recognition and prompt intervention are paramount in mitigating the morbidity and mortality associated with MAS in SLE patients, necessitating a multidisciplinary approach.

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