

Scrub Typhus-Induced Macrophage Activation Syndrome with Flare of Systemic Lupus Erythematosus; A Rare Case Report

ABSTRACT

Aims: Infection is a major trigger for both Lupus flare and Macrophage activation syndrome. Scrub typhus infection associated with lupus flare or MAS has been very rarely reported. We report a case of scrub typhus-induced MAS along with a flare of disease activity in a neuropsychiatric lupus patient presenting after discontinuation of medications.

Presentation of case: 13-year-old girl, a known case of neuropsychiatric lupus with lupus nephritis, on immunosuppressant for the last 1 year had stopped all medications for 3 months. She had presented with a fever and altered sensorium. Based on clinical and laboratory investigations, a diagnosis of scrub typhus-induced macrophage activation syndrome with a flare of lupus disease activity was made and the patient was treated with injection doxycycline and glucocorticoids. There was rapid clinical improvement with treatment.

Discussion: The case emphasizes the importance of identifying the exact trigger behind the deterioration of a patient with lupus and its therapeutic implications. An infection alone requires antibiotics only, flare without infection requires up titrating immunosuppressants but the presence of life-threatening complications like MAS along with infection requires prompt treatment of both facets simultaneously.

Conclusion: Scrub typhus infection should be ruled out apart from other common infections in any patient with lupus flare or MAS.

Keywords: Scrub Typhus, Macrophage activation syndrome, Systemic lupus erythematosus, Lupus

1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that can affect various organs and lead to serious complications. A lupus flare is characterized by an aggravation of existing or remitted symptoms or the appearance of new organ involvement. Macrophage activation Syndrome (MAS) is a rare complication of autoimmune diseases including SLE, with a reported incidence of 0.9-4.6% among SLE patients(1). MAS is a multifarious disease, presenting with signs and symptoms pertaining to various organs like fever, hepatosplenomegaly, hematological manifestations, etc. Here we present a case of a scrub typhus infection-induced lupus flare and MAS in a patient with poor compliance to medications.

2. PRESENTATION OF CASE

A 13-year-old female, diagnosed with systemic lupus erythematosus (SLE) one year back; who was lost to follow-up and stopped all medications for three months presented with high-grade fever (39.5°C) for three weeks and altered sensorium for last two days.

At the age of 12 years, she was diagnosed with Lupus nephritis and Neuropsychiatric SLE associated with autoimmune hemolytic anemia (AIHA). Neuropsychiatric manifestations at that time were in the form of visual hallucinations which were controlled by antipsychotic drugs. Previous records showed DCT-positive anaemia (Hb-6.2gm%), hypo-albuminaemia (2.5gm/dL), proteinuria (24 Hour urine protein 756mg/day) with active sediments, ANA 3+ coarse speckled, with anti-ribosomal P protein 3+ on ANA profile, low complements, and high anti-dsDNA. Renal biopsy showed features of Lupus Nephritis class IIC. She was treated with intravenous immunoglobulin (IVIg) and injection of methylprednisolone (1000mg for 3 consecutive days), followed by oral prednisolone, and injection cyclophosphamide as per NIH protocol.

She was doing well until she stopped medication three months back when she started having high-grade fever. She developed altered sensorium and confusion for two days for which she was brought to medical attention.

On presentation, her GCS was 5/15 (E1V2M2). She had severe pallor, jaundice, tachycardia, and hypotension (blood pressure of 80/50mmHg). On examination there was soft, tender hepatomegaly with mild splenomegaly, bilateral extensor plantar with normal tone and jerks, meningeal signs were absent, and urine output was normal.

Presently, investigations revealed severe haemolytic anemia [Hb-3.9gm%, MCV-116.5fL, corrected reticulocyte count-3.6%, LDH- 13350 IU/L (reference: <250 IU/L)], leukocytosis [TLC-14100cells/cu.mm), neutrophils-48% and lymphocytes-46%] and thrombocytopenia (95000 platelets/ μL). LFT showed indirect hyperbilirubinemia [Total bilirubin-3.9mg/dL, indirect -2.3mg/dL], elevated transaminases [AST- 9012 IU/dL, ALT- 1858 IU/dL (reference <40 IU/dL)]. Inflammatory markers were elevated [CRP-14.43mg/L (reference: <5mg/L), procalcitonin-2.38ng/mL (reference: <0.5ng/mL) and ferritin-1,48,000 $\mu\text{g/L}$ (reference: 12-150 $\mu\text{g/L}$)]. Serum triglyceride was 413mg/dL (reference: <150mg/dL). CPK levels were 1144 $\mu\text{g/L}$ (reference: 10-120 $\mu\text{g/L}$). Her Anti dsDNA levels were elevated (196 IU/mL) [reference <100IU/mL] and complement (C3-18.4mg/dL [reference: 90-180mg/dL] and C4-6.3mg/dL [reference: 10-40mg/dL]) levels were low. Blood for IgM against Hepatitis A and E virus, Leptospira were negative, and anti-HBsAg was negative. Scrub Typhus IgM was positive.

A diagnosis of Scrub Typhus-induced Macrophage activation syndrome (MAS) with lupus flare was made. She was started on injection doxycycline (100 mg twice daily for 10 days) along with injection of methylprednisolone (500mg once daily for 3 consecutive days followed by daily Prednisolone (1mg/kg/day). A packed cell transfusion was done. There was clinical recovery within a couple of days in form of subsidence of fever and improvement in sensorium. Biochemical resolution in form of falling ferritin (1540 $\mu\text{g/L}$), stabilization of blood counts (Hb-9gm%, TLC-10000cell/cu.mm, Platelets-190000cells/ μL), and declining inflammatory markers (CRP-0.765mg/L) and liver enzyme (ALT-115 IU/dL and AST-92 IU/dL) was also seen after 10 days of therapy.

3. DISCUSSION

This case highlights the importance of identifying the exact trigger of Macrophage activation syndrome (MAS) and flare of disease activity in patients with Lupus and its therapeutic implications. There are many factors responsible for the precipitation of a lupus flare like

treatment non-adherence, infection, stress, and exposure to ultraviolet rays. Macrophage activation syndrome which is a hyperinflammatory state is caused by the proliferation and activation of T-cells and macrophages which produce an excessive inflammatory response and hypersecretion of cytokines. Although an identifiable precipitating factor is often not identified, MAS has been related to numerous triggers like infection (e.g., Epstein Barr virus), hematological malignancies (e.g., Lymphoma), or connective tissue diseases like systemic juvenile idiopathic arthritis (SJIA), etc.(2)(3). The traditional HLH 2004 criteria was used to diagnose MAS in this case but serum ferritin level $>10000\mu\text{g/L}$ can be considered a remarkable initial screening tool with a sensitivity of 90% and specificity of 96%.(4)

Sporadic cases of MAS triggered by Scrub typhus infection have been reported globally but mostly from scrub typhus prevalent areas such as India, China, Japan, etc.(5),(6),(7),(8)(9),(10). Infection, MAS, and lupus flare can trigger similar indistinguishable inflammatory responses with fever being a common response in many cases. Here lies the importance of identifying the exact cause of deterioration of a patient with lupus. Infection alone can be treated with antibiotics only whereas an infection-related flare or MAS will require up titrating the immunosuppressant apart from antibiotics. Moreover, immunosuppressants without treating an undiagnosed infectious trigger of MAS or lupus flare can have disastrous consequences. In this context, C-reactive protein is one of the most sensitive and specific markers to identify infection in a patient with lupus. Complement levels and anti-dsDNA antibody titer are other parameters that help in solving the clinical dilemma. CRP is significantly elevated in presence of infection and low complement along with elevated anti-dsDNA is a feature of flare of lupus disease activity. (11),(12)

In our case, the patient had both a high level of CRP and anti-dsDNA as well as low levels of C3 and C4 which lead us to a conclusion of lupus flare with an underlying systemic infection apart from MAS. With other possibilities ruled out, we concluded that Scrub typhus infection was the trigger behind the sequence of events.

4. CONCLUSION

Infectious triggers like scrub typhus should be sought for and treated in any patient with lupus presenting with a flare or life-threatening macrophage activation syndrome as administration of high dose immunosuppressant without addressing the infection can have grave consequences.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

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