

Case Report

Mycobacterium Tuberculosis-Associated Hemophagocytic Syndrome in Systemic Lupus Erythematosus: A Case Report

Sistemik Lupus Eritematözde Mycobacterium Tuberculosis ile İlişkili Hemofagositik Sendrom: Olgu Sunumu

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Mycobacterium tuberculosis infection is a complex, potentially life-threatening disease. Multiple hematological abnormalities may be seen in tuberculosis infection. However, Mycobacterium tuberculosis-associated hemophagocytic syndrome (HPS) in systemic lupus erythematosus (SLE) patients is quite rare. In this article, we report a 47-year-old female case of Mycobacterium tuberculosis-associated HPS in a patient with SLE. The patient had diffuse alveolar hemorrhage, myocarditis, and acute renal failure and required 17 sessions of plasma exchange and six sessions of cyclophosphamide. She also presented with fever, hypotension, desaturation, hepatosplenomegaly, and pancytopenia which required intubation. Broncho-alveolar lavage revealed the diagnosis of Mycobacterium tuberculosis. The patient was initiated with rifampicin, ethambutol, pyrazinamide, moxifloxacin and amikacin. There was no indication of any SLE flare; however she continued to be febrile and pancytopenic. Her ferritin level was observed to be elevated. A bone marrow examination also showed hemophagocytosis plus multiple granulomas. Despite active treatment, the patient died due to septic shock and multi-organ failure. Mycobacterium tuberculosis has the potential to induce HPS in SLE patients; therefore, accurate diagnosis and aggressive therapy are critical. All SLE patients should be screened for latent tuberculosis and managed accordingly.

Key words: Hemophagocytic syndrome; systemic lupus erythematosus; tuberculosis.

Mycobacterium tuberculosis enfeksiyonu, kompleks ve muhtemelen yaşamı tehdit eden bir hastalıktır. Tüberküloz enfeksiyonunda birden çok hematolojik anormallikler görülebilir. Ancak, sistemik lupus eritematöz (SLE) hastalarında Mycobacterium tuberculosis ile ilişkili hemofagositik sendrom (HPS) nadir görülmektedir. Bu yazıda SLE olan ve Mycobacterium tuberculosis ile ilişkili HPS saptanan 47 yaşında bir kadın olgu sunuldu. Hastada difüz alveolar hemoraj, miyokardit ve akut renal yetmezlik vardı ve hastaya 17 seans plazma değişimi yapılması ve altı seans siklofosfamid verilmesi gerekti. Ateş, hipotansiyon, desatürasyon, hepatosplenomegali ve pansitopeni görülen hasta entübe edildi. Bronkoalveolar lavajda Mycobacterium tuberculosis tanısı kondu. Hastaya rifampisin, etambutol, pirazinamid, moksifloksasin ve amikasin başlandı. Sistemik lupus eritematöz alevlenmesine ilişkin herhangi bir endikasyona rastlanmadı; ancak, hastada ateş ve pansitopeni devam etti. Ferritin düzeyinin yükseldiği gözlemlendi. Kemik iliği muayenesinde hemofagositoz artı çoklu granüloma rastlandı. Aktif tedaviye rağmen, hasta septik şok ve çoklu organ yetmezliği nedeniyle kaybedildi. Mycobacterium tuberculosis, SLE hastalarında HPS'yi tetikleyebilir; bu nedenle bu hastalarda doğru tanı ve agresif tedavi önem taşır. Tüm SLE hastaları, latent tüberküloz için taranmalı ve gerektiğinde tedavi edilmelidir.

Anahtar sözcükler: Hemofagositik sendrom; sistemik lupus eritematöz; tüberküloz.

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Hemophagocytic syndrome (HPS) is a hematological phenomenon characterized by the activation of either macrophages or histiocytes that contain prominent hemophagocytosis features in the bone marrow and other reticulo-endothelial systems. This leads to the phagocytosis of white blood cells, red blood cells, platelets, and their precursors. Infections, malignancies, autoimmune diseases, and a variety of other medical conditions can all lead to HPS.^[1]

In systemic lupus erythematosus (SLE) patients, HPS associated with *Mycobacterium tuberculosis* has only been reported once.^[2] Herein, we report a case of an SLE patient who developed HPS due to this type of bacteria.

CASE REPORT

A 47-year-old female was diagnosed with a case of SLE in November 2009 when she first presented with constitutional symptoms, a malar rash, and pancytopenia [white blood cell count 3×10^9 ($3.9-11 \times 10^9$), hemoglobin 8.5 g/l (11-16 g/l), platelet 39×10^9 ($150-400 \times 10^9$)] along with positive antinuclear antibody (ANA), and anti-double-stranded DNA (anti-ds-DNA) antibodies. Her temperature was 36.9 °C, and her blood pressure was 74/45 mmHg. Furthermore, her heart rate was 108 beats/minute, and her respiratory rate was 20 breaths/minute. A chest examination revealed coarse crackles throughout both lungs as well as central and bilateral lung infiltration. The cardiac, abdominal, and neuromuscular exams were unremarkable. The patient was admitted to the intensive care unit (ICU) with diffuse alveolar hemorrhage and was started on pulse methylprednisolone, plasma exchange, and cyclophosphamide. She was also found to have severe mitral valve regurgitation, diffuse myocardial wall suppression, an ejection fraction of 25%, and acute renal failure and received a total of 17 sessions of plasma exchange, three cycles of cyclophosphamide, and several sessions of hemodialysis. After this treatment in December 2009, her ejection fraction improved to 55%, and her mitral valve regurgitation was found to be mild. She then underwent a renal biopsy that showed lupus nephritis class II (mesangial proliferation with mild-to-moderate fibrosis). She was also to complete a total of six cycles of cyclophosphamide every other week.

In February 2010, just a few hours after finishing her last cycle of cyclophosphamide, the patient came to the emergency department complaining of fever and lethargy. Her physical examination

revealed an oral temperature of 38.4 °C, blood pressure of 80/50 mmHg, heart rate of 110 beats/min, respiratory rate of 18 breaths/min, and oxygen saturation of 96% at room air. Chest auscultation revealed coarse crackles, and abdominal palpation was notable for hepatosplenomegaly, which had not been found during her previous admission. She was resuscitated with intravenous fluids and started on broad-spectrum antibiotics plus hydrocortisone. Laboratory investigation showed the following: hemoglobin 10.5 g/l (normal range 11-16 g/l), white blood cell count 1.48×10^9 (normal range $3.9-11 \times 10^9$) with neutrophils at 71%, lymphocytes at 17%, and monocytes at 6%, platelet count 58×10^9 (normal range $140-350 \times 10^9$), lactate dehydrogenase 994 U/l (normal range 135-214 U/l), C-reactive protein (CRP) 273 mg/l (normal range 0-5 mg/l), erythrocyte sedimentation rate (ESR) 55 mm/hr (normal range <15 mm/hr), lactic acid 4.1 mmol/l (normal range 0.5-2 mmol/l), alanine aminotransferase 147 U/l (normal range 10-45 U/l), and aspartate aminotransferase 87 U/l (normal range 10-45 U/l). The electrolytes and urea were normal. A chest X-ray showed widespread bilateral fine nodular shadows, but the patient had no symptoms and signs that indicated an SLE flare-up. Her C3 was 1.05 g/l (normal range 0.9-1.8 g/l), and her C4 was 0.83 g/l (normal range 0.1-0.4 g/l). In addition, the patient's anti-ds-DNA antibody titer was normal.

She was admitted to the ward after resuscitation. Thoracic computed tomography (CT) showed diffuse bilateral centrilobular lung nodules, paraaortic lymph node enlargement, and a small splenic lesion. By the next morning, the patient began to desaturate and required intubation. She was then moved to the ICU where she underwent a bronchoscopy, and a bronchoalveolar lavage sample was positive for acid-fast bacillus. The diagnosis of *Mycobacterium tuberculosis* infection was made, and she was started on rifampicin, ethambutol, pyrazinamide, moxifloxacin, and amikacin. All other cultures (blood and urine) were negative. Tests for brucella titer and hepatitis B and C were negative, and viral serology for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV) also came back negative. Additionally, her fungal culture was also negative.

The patient, however, continued to be febrile and pancytopenic, and a suspicion of HPS was raised due to a ferritin level of 6.800 ug/l (normal range 15-150 ug/l). The patient underwent a bone marrow biopsy and aspiration which showed that her cellular

marrow was infiltrated with abnormal histiocytes plus multiple granuloma consistent with hemophagocytosis (Figures 1 and 2). Therefore, HPS associated with *Mycobacterium tuberculosis* was diagnosed. Although she was on antituberculous medication and broad-spectrum antibiotics, the patient developed septic shock and multi-organ failure which resulted in her death.

DISCUSSION

Although rare, HPS can occur in both active and inactive cases of SLE, but the majority take place during active SLE. Most instances of HPS in inactive SLE are thought to be related to immunosuppressive drugs,^[3,4] and several viral, bacterial, fungal, and parasitic infections have also been found to be associated with HPS.

Hemophagocytic syndrome is a potentially life-threatening, aggressive disease that manifests clinically with fever, lymphadenopathy, jaundice, hepatosplenomegaly, and bleeding tendency. Laboratory tests may show pancytopenia, elevated ferritin and lactate dehydrogenase levels, and disseminated intravascular coagulopathy (DIC). Diagnosis is confirmed by a bone marrow biopsy that shows hemophagocytosis. The mechanism of HPS is not well known. The immune complex deposits hematopoietic cells on the bone marrow and produces autoantibodies. These autoantibodies react with the hematopoietic cells, and then the histiocytes phagocytose these cells. Interleukin-1 (IL-1), tissue necrosis factors- α (TNF- α) and interferon- γ (INF- γ) are reported to be important for histiocyte activation

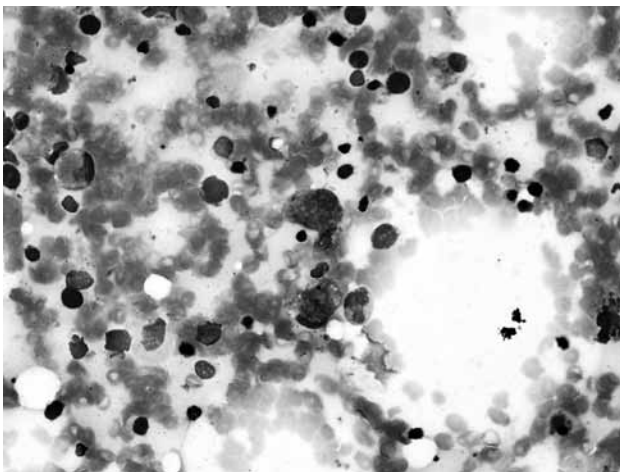


Figure 1. Bone marrow aspirate showing multiple hemophagocytic cells engulfing some erythroid cells, granulocytes, and platelets (Wright-Giemsa stain x 600 magnification).

and the pathogenesis of HPS.^[5,6] When HPS is a manifestation of SLE, it is treated with high-dose corticosteroids. In one patient with SLE, plasma exchange was used for treatment of HPS.^[7] In addition, pathogen-directed therapy is indicated in HPS cases caused by infection.^[4,5]

In patients with SLE, two cases of mycobacteria have been reported that were associated with HPS. The first case was a 15-year-old girl with SLE who was diagnosed with HPS associated with *Mycobacterium avium* complex (MAC). Her SLE was inactive, and she responded poorly to initial treatment with corticosteroids and intravenous immunoglobulins. However, following treatment with clarithromycin, amikacin, and ciprofloxacin, she improved gradually and was discharged.^[5] The second case, a 36-year-old woman, was initially thought to have acute lupus hemophagocytic syndrome. However, increased levels of CRP led to further investigation. A Ziehl-Neelsen stain of the buffy coat showed acid-fast bacilli in the phagocytic cells, and the diagnosis of HPS associated with *Mycobacterium tuberculosis* was confirmed by blood cultures and polymerase chain reaction. She died despite active treatment.^[2] Our case is the second case of HPS in inactive SLE caused by *Mycobacterium tuberculosis*. Our patient's characteristics were compared to the characteristics of the two patients in the preceding cases and are presented in Table 1.

As our case and a review of the literature demonstrate, HPS in SLE is an aggressive disease regarding both flare-ups and conditions related to infection. *Mycobacterium tuberculosis* should be considered in the differential diagnosis of the organisms

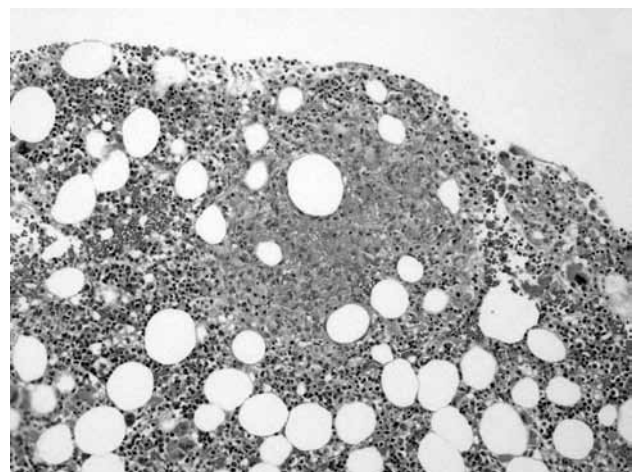


Figure 2. Bone marrow biopsy showing abnormal epithelioid granuloma with focal necrosis (H-E x 200).

Table 1. Review and comparison between the reported cases of hemophagocytic syndrome associated with *Mycobacterium tuberculosis* in systemic lupus erythematosus patients

Cases	Our case	Reference No. 5	Reference No. 2
Age and gender	47-year-old female	15-year-old female	36-year-old female
Clinical presentation	Fever, hepatosplenomegaly, pancytopenia, high ferritin level, and chest infiltrates.	Fever, hepatosplenomegaly, pancytopenia, and high ferritin level.	Fever, lymphadenopathy, and pancytopenia.
Mycobacterial species	<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium avium</i> complex	<i>Mycobacterium tuberculosis</i>
Method of diagnosis and laboratory investigation	Acid-fast bacilli in the broncho-alveolar lavage. Bone marrow showed granuloma with hemophagocytosis	Bone marrow showed non-caseating granulomatosis. <i>Mycobacterium avium</i> complex in gastric lavage.	Hemophagocytosis and acid-fast bacilli in the peripheral blood smear.
Syndrome in systemic lupus status	Inactive	Inactive	Inactive
Treatment	Rifampicin, ethambutol, pyrazinamide, moxifloxacin, and amikacin.	Corticosteroids and IV immunoglobulin initially, then amikacin, ciprofloxacin, and clarithromycin.	Not mentioned
Outcome	Death	Discharge	Death

that can cause HPS in SLE. We recommend that any SLE patient should be examined for the presence of latent *Mycobacterium tuberculosis* prior to initiating immunosuppressive therapy, especially in endemic areas. In one study, it was found that the use of isoniazid prophylaxis in such patients decreased the incidence of tuberculosis from 11% to 2%.^[8] The published literature suggests that T-cell interferon-gamma release assays (IGRAs) have a better diagnostic sensitivity to diagnose latent *Mycobacterium tuberculosis* than tuberculin skin testing (TST) in patients with immune-mediated inflammatory diseases.^[9] Once confirmed, accurate treatment should be strongly considered.

Declaration of conflicting interests

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