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Hemophagocytic Lymphohistiocytosis in a Patient with Disseminated Tuberculosis

Dissemine Tüberkülozlu Bir Hastada Hemofagositik Lenfohistiyositoz

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease associated with multi-organ involvement. Infections, autoimmune disorders, and neoplasms can lead to secondary HLH. Herein, we report the case of a patient who presented with fever, jaundice, and pancytopenia and was diagnosed to have disseminated tuberculosis with HLH. Hemophagocytic lymphohistiocytosis should be considered in patients presenting with fever, rash, lymphadenopathy, hepatosplenomegaly, neurologic symptoms, cytopenia, elevated serum ferritin level, and deranged liver function tests. As the mortality rate is very high in patients with HLH, prompt diagnosis and treatment of the underlying disease and secondary HLH is critical for a good outcome.
Keywords: Tuberculosis, hemophagocytic lymphohistiocytosis, disseminated tuberculosis

Öz

Hemofagositik lenfohistiyositoz (HLH), çoklu organ tutulumuyla seyreden yaşamı tehdit eden bir hastalıktır. Enfeksiyonlar, otoimmün bozukluklar ve neoplazmalar ikincil HLH'ye yol açabilir. Ateş, sarılık ve pansitopeni ile başvuran ve HLH ile dissemine tüberküloz tanısı alan bir hasta bu yazıda sunulacaktır. Ateş, döküntü, lenfadenopati, hepatosplenomegali, nörolojik semptomlar, sitopeni, serum ferritin yüksekliği ve karaciğer fonksiyon testlerinde bozulma ile başvuran hastalarda HLH düşünülmelidir. Hemofagositik lenfohistiyositozlu olgularda mortalite oranı çok yüksek olduğundan, altta yatan hastalık sürecinin ve sekonder HLH'nin hızlı tanı ve tedavisi, HLH'li hastalarda iyi tedavi sonuçları açısından kritik öneme sahiptir.
Anahtar Kelimeler: Tüberküloz, hemofagositik lenfohistiyositoz, dissemine tüberküloz

Introduction

Neoplasms, infections, or autoimmune conditions can lead to secondary hemophagocytic lymphohistiocytosis (HLH), and approximately one-third of the cases have more than one underlying cause[1]. Hemophagocytic lymphohistiocytosis has been reported as a rare complication of tuberculosis. *Mycobacterium tuberculosis* primarily affects the lungs and can cause multiple short- and long-term complications.

Hemophagocytic lymphohistiocytosis is a life-threatening disease which involves multiple organs. It is characterized by hemophagocytosis in the bone marrow, lymph node, spleen, or liver. Secondary HLH is usually associated with malignancies, autoimmune disorders, or infections. Hemophagocytic lymphohistiocytosis is associated with bacterial infections, such as those caused by *Mycobacterium tuberculosis*, and viral infections, such as those caused by the Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, parvovirus, herpes simplex virus, measles virus, dengue virus, and human

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immunodeficiency virus (HIV). Patients with underlying autoimmune diseases, neoplasms, or infections who present with fever, rash, lymphadenopathy, hepatosplenomegaly, neurological symptoms, elevated serum ferritin level, and deranged liver function test should be evaluated for HLH[2]. Although HLH has been reported in several patients with tuberculosis, majority of the patients had other comorbidities, including HIV infections, autoimmune disorders, or malignancies. The mortality rate is approximately 50%, and most patients have not been followed up long-term. Additionally, the treatment administered, including the type and dose of immunomodulators used or the trial of steroid treatment, has not been mentioned in most reports because of the lack of consensus regarding the treatment of HLH secondary to tuberculosis. In this case report, we have presented a 28-year-old female without any comorbidities who was diagnosed to have disseminated tuberculosis with HLH and was followed up for one year. She demonstrated significant improvement with the administration of anti-tuberculosis drugs and steroids.

Case Report

A 28-year-old female from Punjab, India, presented with complaints of fever for two weeks. Her temperature was approximately 37.2 °C-38.6 °C. The patient also reported decreased appetite and abdominal discomfort for two weeks. The patient developed yellowish discoloration of the sclera and skin five days prior to presentation. She did not report any history of tuberculosis in the past or her family. The patient had been previously vaccinated for tuberculosis. However, she did not have any recent history of vaccination. On examination, the patient was icteric, and her body temperature was 38.7 °C. Auscultation revealed decreased breath sounds in both the infrascapular regions. The abdomen was soft on palpation. The spleen was palpable 2 cm below the left costal margin, and the liver was palpable 5 cm below the right costal margin. Abdominal percussion revealed shifting dullness. There were no other significant findings on examination. Blood investigations revealed pancytopenia. Her blood parameters were as follows: hemoglobin, 8.5 g/dl (normal range: 12.0-15.5 g/dl); total leucocyte count (TLC), 3.7×10^9/l (normal range: 4.5-11.0$\times10^9$/l); platelet count, 4000×10^9/l; corrected reticulocyte count, 0.1%; aspartate transaminase, 465 IU/ml (normal range: 4-32 U/l); alanine transaminase, 420 IU/ml (normal range: 4-33 U/l); total bilirubin, 7.1 mg/dl (normal range: 0.1-1.2 mg/dl); direct bilirubin, 4.5 mg/dl (normal range: <0.3 mg/dl); alkaline phosphatase, 415 IU/l (normal range: 30-120 IU/l); gamma-glutamyl transferase, 298 U/l (normal range: 5-40 U/l); total protein, 4.9 mg/dl (normal range: 6.0-8.3 g/dl); albumin, 2.2 mg/dl (normal range: 3.5-5.5 g/dl); erythrocyte sedimentation rate, 3 mm/h; C-reactive protein, 72 mg/l (normal: <10 mg/l); and lactate dehydrogenase (LDH), 732 U/l (normal range: 140-280 U/l). Her blood culture and urine culture did not yield any growth. Blood tests to rule out other infectious diseases were negative. Reverse-transcriptase polymerase chain reaction for Coronavirus disease-2019, tests for dengue non-structural protein-1 antigen, dengue IgM, dengue IgG, scrub typhus serology, leptospira antigen, leptospira serology, and malarial antigen, films for malarial parasite, Weil-Felix test, and Widal test were negative. Screening for HIV, hepatitis B surface antigen, and hepatitis C virus was negative. Contrast-enhanced computed tomography (CT) scan of the abdomen showed moderate ascites and multiple portal, peripancreatic, para-aortic, aorto-caval, and mesenteric lymph nodes. It also revealed hepato-splenomegaly, bilateral pleural effusion, and mild circumferential thickening of the terminal ileum, ileocecal junction, cecum, and ascending colon. The imaging findings were suggestive of abdominal tuberculosis. High-resolution CT scan of the chest revealed bilateral pleural effusion and fibrotic calcified bands with bronchiectasis in the right upper lobe, suggestive of a prior granulomatous infection. One unit of platelets from a single donor and eight units of platelets from another random donor were transfused into the patient because her platelet counts were persistently low (<10,000/l). Ascitic fluid analysis revealed a white blood cells of 160 (20% polymorphs and 80% lymphocytes). Staining for acid-fast bacilli and culture for *Mycobacterium tuberculosis* were both negative. The ascitic fluid albumin level was 1.4 mg/dl, and serum albumin-ascitic fluid albumin gradient was low (0.8). Cartridge-based nucleic acid amplification test for *Mycobacterium tuberculosis* using the ascitic fluid was negative. Bone marrow biopsy revealed prominence of histiocytes, hemophagocytosis of the marrow elements, and associated granulomatous inflammation. Smear of the biopsy material demonstrated acid-fast bacilli. Bone marrow culture demonstrated growth of *Mycobacterium tuberculosis*. The serum triglyceride (278 mg/dl; normal range: <150 mg/dl) and ferritin (771 ng/ml; normal range: 10-120 ng/ml) levels were elevated. The fibrinogen level was 440 mg/dl (normal range: 200-400 mg/dl). The diagnosis of HLH was considered in view of the fever, pancytopenia, splenomegaly, hepatomegaly with a deranged liver function test, elevated ferritin (>500 ng/ml) and LDH levels, and bone marrow findings. The H-score was 203, which indicated a 88-93% probability of HLH[2,3]. Thus, the patient was diagnosed to have disseminated tuberculosis with secondary HLH.

The patient was administered anti-tuberculosis treatment with rifampicin, isoniazid, pyrazinamide and ethambutol. Considering the weight of the patient was 62 kg, she was administered 600 mg of rifampicin, 450 mg of isoniazid, 1.5 g of pyrazinamide, and 1.2 g of ethambutol, once daily. As the clinical condition of the patient stabilized, dexamethasone was administered for the treatment of HLH. Initially, 8 mg dexamethasone was

administered every 8 hours for three days. Thereafter, the steroid dose was tapered and stopped over the next two weeks. Administration of anti-tuberculosis treatment and steroids resulted in a gradual decrease in the TLC and platelet count until they became normal. Five days after initiation of anti-tuberculosis treatment and steroids, the TLC was 8.7×10^9/l and the platelet count was $2,35\times10^9$/l. The patient became afebrile, her abdominal symptoms resolved, and her liver function test results returned to normal.

On follow-up, the patient remained asymptomatic, and her complete blood count was normal. Two months after discharge, the patient remained asymptomatic, with normal laboratory test parameters. The continuation phase of the anti-tuberculosis treatment with rifampicin, isoniazid and ethambutol was administered to the patient. The total duration of the anti-tuberculosis treatment was six months. At the one year follow-up, the patient was asymptomatic and the hematological and biochemical parameters were normal.

Discussion

Hemophagocytic lymphohistiocytosis is a life-threatening disease characterized by excessive T-cell and macrophage activation and is associated with the impaired ability of natural killer (NK) cells and cytotoxic T-lymphocytes to kill the target cells. Hemophagocytic lymphohistiocytosis can be diagnosed based on the criteria published in the HLH-2004 trial[4]. HLH-94 was the first prospective international study on HLH, which used the following five criteria for the diagnosis: fever, bicytopenia, splenomegaly, elevated triglyceride levels or hypofibrinogenemia, and hemophagocytosis[5]. The following additional criteria were introduced in the HLH-2004 trial: high soluble interleukin-2 receptor levels, hyperferritinemia, and low/absent NK-cell-activity. Five out of the eight criteria must be fulfilled to make a diagnosis of HLH. The HLH-2004 diagnostic criteria was fulfilled in our patient. However, as these guidelines were first developed to diagnose the primary forms of HLH in children, different parameters, such as the H-score, have been studied and validated for the diagnosis of reactive forms of HLH in adults[2,3,6]. The H-score corresponds to a weighted criteria and it provides a better assessment of the patients' risk of having HLH.

Among the autoimmune disorders, systemic lupus erythematosus (SLE) and adult-onset Still's disease are frequently associated with HLH. Systemic lupus erythematosus association with HLH have been reported more frequently than adult-onset Still's disease's association with HLH (133 vs. 54); however, the prevalence is higher in adult-onset Still's disease (12%) than in SLE (4%). Hemophagocytic lymphohistiocytosis has also been reported among patients with systemic vasculitis, rheumatoid arthritis, or inflammatory bowel disease. Infections and less commonly the use of concurrent medications are frequent triggers of HLH in such patients[1,7]. Hemophagocytic lymphohistiocytosis reportedly affects 1% of adults with hematological cancer. It may affect approximately 20% of patients with some types of B-cell (patients without peripheral adenopathies or intravascular forms) and T-cell (panniculitis-like or nasal NK-cell) lymphomas[8].

Because our patient was from a tropical country and had presented with fever, the patient was initially evaluated for common infections such as tuberculosis, dengue (fever and pancytopenia), rickettsia (fever, pancytopenia, hepatosplenomegaly, deranged liver function test), malaria (fever, jaundice and pancytopenia), and viral hepatitis (fever followed by jaundice). Her chest X-ray revealed nonhomogenous infiltrates in the right upper and mid zones. High-resolution CT of the chest was obtained to look for any evidence of tuberculosis. A contrast-enhanced CT scan of the abdomen was obtained to look for abdominal tuberculosis, liver abscesses, or malignancy because her blood tests for infections yielded negative results. At this stage, a possible diagnosis of tuberculosis/disseminated tuberculosis/HLH or hematological malignancy was considered. Bone marrow aspiration and biopsy was performed, which confirmed the diagnosis of disseminated tuberculosis with HLH. Among patients with tuberculosis, 15-20% are diagnosed with extra-pulmonary tuberculosis[9]. Among patients with extra-pulmonary tuberculosis, 35% are diagnosed with tuberculous lymphadenitis, 20% with plural tuberculosis, 10% with tuberculosis of the bone marrow, and 9% with genitourinary tuberculosis. Other types of extra-pulmonary tuberculosis such as cerebrospinal, abdominal, and cutaneous tuberculosis accounts for 26% of the cases[10]. Although molecular tests offer a quick way of diagnosing tuberculosis, several studies have shown that the accuracy of such tests varies significantly according to the bacillary load and specimen type. The specificity and sensitivity of the molecular tests for pleural tuberculosis is reportedly 99.1% and 46.4%, respectively. The sensitivity and specificity of the molecular tests for lymph node tuberculosis is reportedly 83.1% was 93.6%, respectively, and those for meningeal tuberculosis are 80.5% and was 97.8%, respectively[9].

Among patients with secondary HLH, those who are clinically stable may respond to treatment of the triggering condition alone. The major triggering conditions are infections, rheumatologic conditions, and lymphoid malignancies. Deterioration during therapy for the underlying condition is an indication to administer HLH-specific therapy immediately[11].

Among patients with tuberculosis and secondary HLH, early diagnosis and prompt treatment is necessary as the disease is associated with high mortality. Infections such as tuberculosis are reportedly associated with HLH. Thus, the possibility of HLH should be considered in patients suspected to have or

diagnosed with tuberculosis if they present with bicytopenia or pancytopenia and demonstrate organomegaly and deranged liver function tests. Studies have shown that delayed diagnosis and treatment result in a significant increase in mortality among patients with tuberculosis and HLH. Padhi et al.[12] have reported the administration of anti-tuberculosis treatment alone or in combination with immunosuppressive agents or immunomodulators for the treatment of tuberculosis and HLH. Cyclosporine, etoposide, vincristine, chlorambucil, and fludarabine were used as immunomodulators. Steroids or immunoglobulins were used as immunosuppressive agents.

Conclusion

In our case, the patient was clinically stable. Thus, our patient responded to the treatment of the underlying condition with a trial of steroids, as previously reported[12,13]. In our patient, the TLC and platelet count began to improve the day after initiation of steroids. The TLC returned to normal by the second day, and the platelet count was $1,32\times10^9$/l on the third day. The clinical condition of the patient was closely monitored. Because the patient's clinical condition and laboratory test parameters improved significantly with the administration of steroids and there is a lack of consensus regarding the use of immunomodulators, other immunomodulators were not considered. Among the reported cases of patients diagnosed with tuberculosis and HLH who did not survive, treatment failure was attributed to a delay in the diagnosis and initiation of treatment. Further studies are warranted among patients with tuberculosis and secondary HLH due to the lack of consensus regarding the treatment.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M.A., N.K., E.S., Concept: A.M.A., N.K., E.S., Design: A.M.A., N.K., Data Collection or Processing: A.M.A., N.K., E.S., Analysis or Interpretation: A.M.A., N.K., Literature Search: A.M.A., N.K., E.S., Writing: A.M.A.

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