

Case Report

Undiagnosed tuberculosis associated with hemophagocytic lymphohistiocytosis due to improper use of corticosteroid

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Abstract

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening hematologic disease segregated into familial (primary) and acquired (secondary) subtypes. Hyperinflammation and HLH occur when the immune system fails to clear activated macrophages and histiocytes. Infections, malignancies, and rheumatologic disorders are the major triggers leading to HLH. Miliary tuberculosis is a serious disease with a lymphohematogenous spread of *Mycobacterium tuberculosis*, which is known to be one of the causative agents of HLH. Miliary tuberculosis and HLH have atypical presentations which are similar to routine diseases. Hence, physicians may face challenges to diagnose and treat these complications.

Case report: We report the case of a 60-year-old man with a history of prolonged fever, shortness of breath, jaundice, altered mental status, undiagnosed lower back pain, and overuse of parenteral betamethasone. Miliary tuberculosis was diagnosed by diffuse, vague random micronodules in both lungs and positive acid-fast bacilli in bronchoalveolar lavage and bone marrow aspiration and biopsy. Moreover, compatible presentation and pancytopenia, hypertriglyceridemia, high serum level of ferritin and fibrinogen-derived products, and evidence of hemophagocytosis on bone marrow aspirate led to the diagnosis of HLH. Unfortunately, despite nearly two months of an anti-tuberculosis regimen (standard and salvage) and eight doses of etoposide, he eventually passed away after clinical improvement.

Conclusions: Irrational and indiscriminate use of glucocorticoids can be a devastating cause of the spread of tuberculosis and its rare complications, such as HLH.

Key words: hemophagocytic lymphohistiocytosis, miliary tuberculosis, *Mycobacterium tuberculosis*, treatment.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hematologic disease that occurs with an over-activated or dysregulated immune response. The disorder appears to be inherited through genes or acquired primarily in adulthood [1]. Previously, the disease was divided into primary and secondary types, but recent studies have introduced a new classification [2]. Familial or primary HLH primarily affects infants, but can also occur in adults. The secondary or acquired type (also hereditary type) of HLH occurs secondary to several serious conditions [1,2]. The most common triggers for HLH are infections, malignancies, immune

deficiency syndromes, rheumatologic disorders, and drugs [1,2]. The inability of cytotoxic T cells and natural killer cells to eliminate macrophages leads to hyperinflammation and multiple organ damage [1]. Cytokine storm is another factor that precedes HLH and organ failure [2]. HLH is commonly known as a disease of infancy, but it can occur at any age [1,3].

Patients mainly present with fever, organomegaly (lymphadenopathy, hepatomegaly, and/or splenomegaly), cytopenia, altered mental status, hypertriglyceridemia, hypofibrinogenemia, and hemophagocytosis. HLH shows very high levels of ferritin and low or absence of natural killer (NK) cell

activity. In addition, elevated levels of cytokines and soluble CD-25 are other indicators of HLH. Abnormal liver function tests, jaundice, and abnormal coagulation are seen in these patients [1-3]. The clinical manifestations of HLH have some differences between adults and infants [1].

Tuberculosis (TB) is a serious disease that can cause HLH in adults [1,5]. Despite the worldwide reduction in TB incidence, the disease is still endemic in some regions, particularly in developing countries [6]. HLH due to tuberculosis occurs in 38% of HLH patients due to bacterial infection. This represents 9% of adult HLH cases. There is no definite data on the incidence of HLH in adults; however, it is thought that about 1 in 2000 patients admitted to tertiary medical centers are affected [1,2]. Miliary TB is a potentially fatal subtype of TB that is disseminated through blood and lymph. Some common symptoms of miliary TB are fever which persists for several weeks, chills and rigors, night sweats, weight loss, cough, and specific findings of involving organs [5,7]. Daily spikes in morning fevers are noted to be characteristic of miliary TB [7,8]. Miliary TB in children often presents with hepatosplenomegaly and peripheral lymphadenopathy. Night sweats and hemoptysis are rare in children [7]. Multi-organ damage is the most important consequence of miliary TB. The diagnosis of HLH and miliary TB is a challenging issue because of the similarities in clinical features of various conditions, including liver failure, systemic infections, and hematologic malignancies, [1,2,5,7].

The diagnostic criteria used in the HLH-2004 trial and the H-score are often used to help physicians diagnose HLH with more certainty [3,4] (Table 1). The following studies showed that the H-score is more sensitive and specific than the HLH-2004 criteria for diagnosing HLH, especially in children [2]. Peripheral blood smears (PBS) and bone marrow aspirates from

HLH patients show macrophages containing erythrocytes, platelets, and their precursors [1-3]. Due to the serious and life-threatening nature of HLH, treatment should be initiated as soon as possible with suspicion, regardless of the fulfillment of the criteria [3].

However, there are some reports of HLH in our country such as our previously reported case of nephrotic syndrome with HLH in 2012 [9]. We now present an adult patient with HLH secondary to tuberculosis who was referred to our hospital with a misdiagnosis of severe liver failure with a history of undiagnosed back pain and glucocorticoid overuse as a first case report of HLH-TB in Iran.

Case report

A 60-year-old man was referred to our center with newly diagnosed suspected cirrhosis and fever. Upon admission, the patient was delirious, agitated, and febrile and he had jaundice, tachypnea, cyanosis and oxygen saturation of 57% when breathing in ambient air.

His daughter, as the only source of his medical history, reported that he had no significant medical history until 4 months ago when he developed progressive lower back pain (LBP). LBP was progressively worsening and gradually debilitating, which led to stopping his career as a construction worker. He was then examined at a private clinic and pain was relieved with intramuscular betamethasone LA and high doses of diclofenac and celecoxib. Therefore, he continued to use the above medications intermittently for pain relief. A few weeks later, he developed fever, chills, loss of appetite, and severe weakness. Two weeks before his referral to our center, he was hospitalized due to developing dyspnea and altered mental status. In primary evaluation, he had a fever, jaundice, uremia, and L2-L3 spondylodiscitis

Table 1. HLH-2004 guidelines for the diagnosis of hemophagocytic lymphohistiocytosis (HLH). Diagnosis of HLH in 2004 protocol is based on molecular detection and/or fulfillment at least 5 of the 8 criteria mentioned [14].

Molecular diagnosis	Fulfillment 5 of 8 below criteria
Detection of genes involved in predisposition of HLH	Fever ≥ 38.5 °C Splenomegaly Peripheral blood cytopenia, with at least two conditions below a. Hb < 9 g/dL (for infants < 4 weeks, Hb < 10) b. Platelets < 100000 /mL c. Absolute neutrophil count < 1000 /mL Hypertriglyceridemia (fasting TG > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL) Hemophagocytosis in bone marrow, spleen, lymph node, or liver Ferritin > 500 ng/mL Low or absent NK-cell activity Soluble CD-25 ≥ 2400 U/mL

TG: triglyceride; NK: natural killer.

(Figure 1). Sepsis was suspected and he had received meropenem 1 g intravenous (IV) injection and a tablet of metronidazole 250 mg three times a day (TDS). He was eventually referred to our center because of persistent fever, progressive dyspnea, worsened mental status, cytopenia, and critical illness.

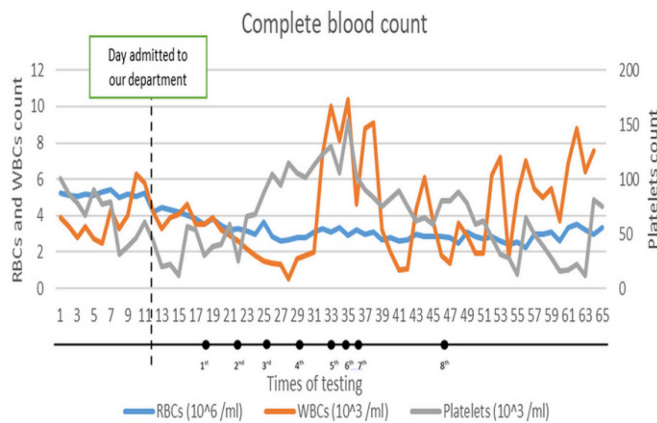
On admission, hypoxic respiratory failure, diffuse crackles and stupor, pancytopenia, increased liver enzymes, and direct bilirubinemia were prominent findings (Figures 2-4). Palmar erythema, spider angioma, splenomegaly, caput medusa, and petechiae/purpura rashes were not found in consideration of liver cirrhosis. Moreover, high resolution computed tomography (HRCT) scan of both

Figure 1. Magnetic resonance imaging (MRI) shows spondylodiscitis in the patient.



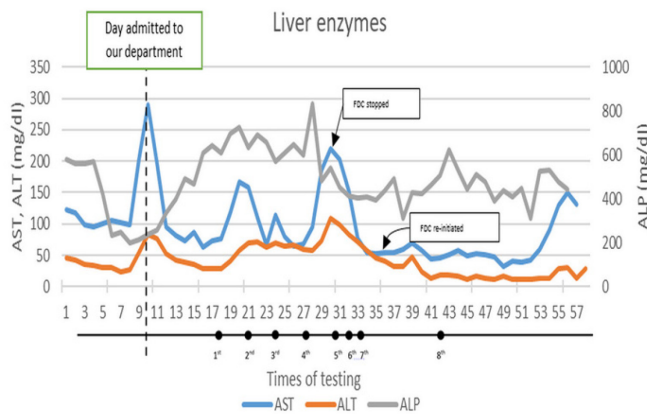
lungs showed bilateral disseminated random micronodular infiltrations (Figure 5). Serum ferritin, fibrinogen-derived products, and fibrinogen levels were 3617 mcg/L, more than 20 mcg/mL, and 299 mg/dL, respectively. The patient's H-score was 218, indicating a 96% probability of HLH according to the H-score criteria [4]. He was admitted to the intensive care unit and intubated due to progressive respiratory failure. Anti-TB first-line drugs as four fixed-dose combinations (FDC) of rifampicin/isoniazid/pyrazinamide/ethambutol (150

Figure 2. Diagram showing levels of CBC during admission. The numbers and timing of given etoposides are shown under the horizontal axis.



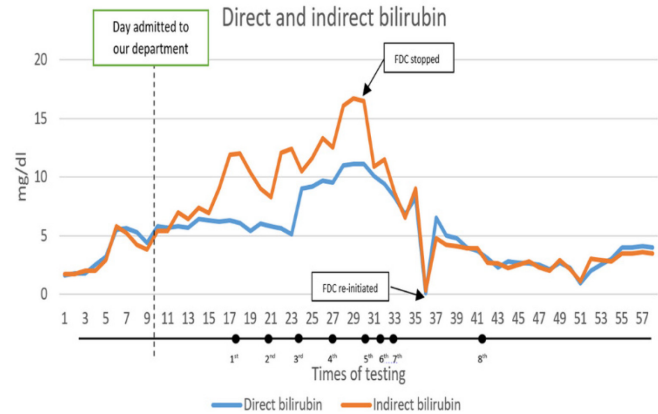
CBC: complete blood count; WBC: white blood cell; RBC: red blood cell.

Figure 3. Diagram showing levels of liver enzymes during admission. Days of stopping and re-initiating of FDC are shown. The numbers and timing of given etoposides are shown under the horizontal axis.



ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; FDC: anti-TB fixed dose combination

Figure 4. Diagram showing bilirubin (direct and indirect) levels during admission. Days of stopping and re-initiating of FDC are shown. The numbers and timing of given etoposides are shown under the horizontal axis.



FDC: anti-TB fixed dose combination.

mg/75 mg/400 mg/275 mg film-coated tablets) and pyridoxine 20 mg daily, and IV dexamethasone 4 mg twice daily were initiated with a presumptive diagnosis of disseminated hematogenous tuberculosis and HLH. The patient had profound confusion, respiratory failure, and critical condition. Therefore, before reliable serum and tissue levels of standard FDC anti-TB, we decided to start parenteral linezolid 600 mg/daily, amikacin 1 g daily, clavulanate-amoxicillin 125/500 mg twice daily with meropenem 500 mg twice daily, and levofloxacin 750 mg daily as a salvage regimen for tuberculosis along with standard oral anti-TB drugs.

Ziehl–Neelsen on bronchoalveolar lavage (BAL) detected acid-fast bacilli. Real-time polymerase chain reaction (PCR) was performed on BAL. *M. tuberculosis* detection was based on the amplification of a specific multi-copy insertion sequence IS6110 and the measurement of fluorescence increase. Furthermore, bone marrow biopsy confirmed acid-fast bacilli and multiple necrotizing granuloma involving cellular bone marrow. Bone marrow aspiration cytology revealed evidence of hemophagocytosis and macrophages engulfing erythrocytes, erythroid precursor, platelets, and neutrophils (Figures 6 and 7).

Ultrasound studies of the liver, biliary tract, and spleen were normal. Etoposide 80 mg IV was added to dexamethasone according to HLH-2004 protocol [3] because of the deteriorating condition of the patient. The second dose of etoposide was prescribed three days later. After the first and second doses of etoposide, platelet count increased, red and white blood cells count decreased, and one week later, salvage anti-TB was discontinued and oral FDC was maintained.

Figure 5. A high-resolution computed tomography (HRCT) scan shows randomly disseminated micronodules in both lungs.

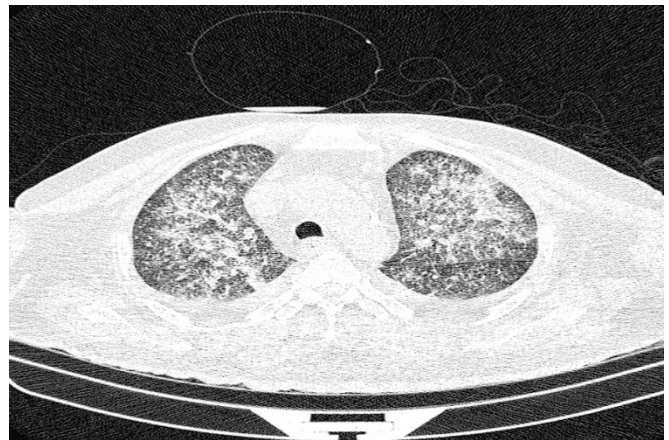


Figure 7. Bone marrow biopsy showing acid-fast bacilli.

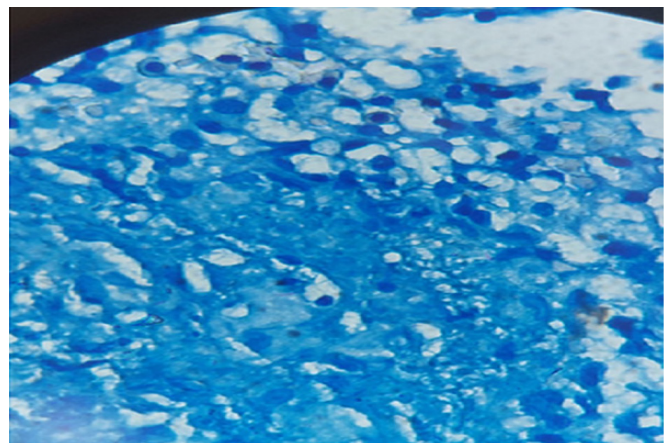
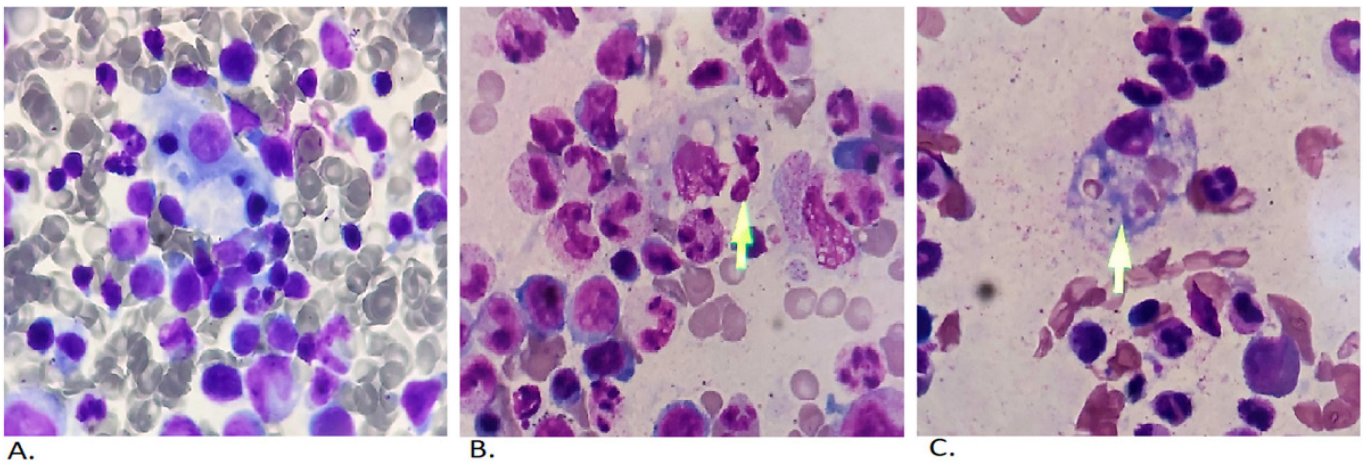


Figure 6. Bone marrow aspiration smear showing hemophagocytosis.



A: hemophagocytosis of erythroid precursors; **B:** hemophagocytosis of neutrophil (arrow); **C:** hemophagocytosis of red blood cell (RBC) and platelets (arrow).

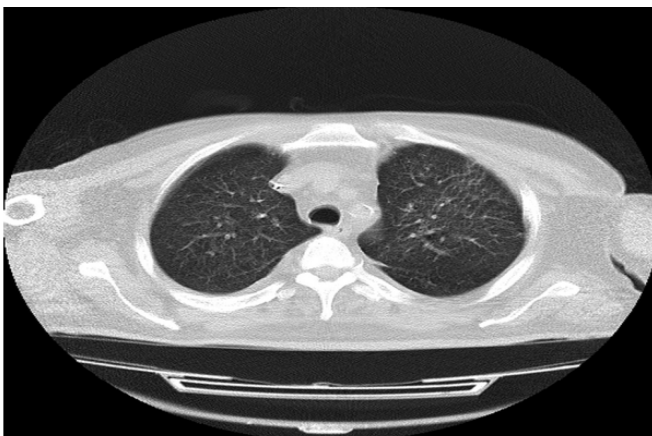
The respiratory function and consciousness improved dramatically during 55 days and he was extubated and started oral feeding. Then, he had complete orientation and confirmed the accuracy of all his medical history before admission to this hospital and loss of consciousness.

The patient received granulocyte colony stimulating factor (G-CSF), platelet, and packed red blood cells multiple times to control cytopenia and coagulation abnormality secondary to etoposide. Approximately 2 weeks later, when bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) increased sharply, administration of oral anti-TB was discontinued (Figure 6), and salvage parenteral anti-TB was reinitiated. Six days after discontinuing FDC, liver function test (LFT) and bilirubin were sufficiently reduced to allow the resumption of first-line therapy, as recommended by the World Health Organization (WHO) [10]. Imipenem 500 mg IV four times a day and a tablet of spironolactone 25 mg daily were added. Computed tomography (CT)-guided bone biopsy of lumbar bone after two weeks of anti-TB was available due to the condition of the patient and it was not remarkable.

Ultimately, the patient received 8 doses of etoposide (each dose includes 80 mg etoposide with normal saline 500-1000 mL for an hour). Laboratory findings and symptoms improved and the patient was stable. The patient's shortness of breath improved and his symptoms disappeared. The repeated HRCT of the lung showed a dramatic decrease in infiltrations (Figure 8).

Unfortunately, despite the clinical improvement, he suddenly became asystole for an unknown reason since sepsis, organ failure, and recurrence of the disorder were ruled out in investigations after recovery. Finally,

Figure 8. High resolution computed tomography (HRCT) scan repeated after improving symptoms showed cleared lungs of micronodules.



he passed away after performing cardiopulmonary resuscitation (CPR) according to American Heart Association (AHA) guidelines [11].

Discussion

HLH is an uncommon serious hematologic disease that results from hyperinflammatory or dysregulated immune system responses. Both familial and acquired HLH are presented with the same triggers. The most common trigger is infections. Among viral infections, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella-zoster virus are more likely to cause HLH. Bacterial infections such as tuberculosis, brucellosis, and Gram-negative species can cause HLH. Tuberculosis is a serious disease that causes significant complications and can lead to HLH, especially in genetically predisposed people [1,2]. The global incidence of tuberculosis is declining, but there are endemics especially in east Asian and African countries [6].

Some conditions make people more susceptible to miliary TB than others. One of these conditions is glucocorticoid use [5]. In our case, the patient had been using glucocorticoids for a long time and had been infected by miliary TB. Moreover, we faced a misdiagnosis and several unsuccessful efforts. He had developed multiple organ failure and had acute dyspnea with SpO₂ of 57%, systemic cyanosis, and severe mental status disturbance. HLH was suspected during the evaluation of the patient who had not responded to antibiotics; hence etoposide was started as soon as possible. The patient had prolonged fever, cytopenia, hypertriglyceridemia, high ferritin levels, jaundice, and hemophagocytosis (6 out of the 8 diagnostic criteria of HLH-2004 [3]) and an H-score of 218. NK cell activity and sCD-25 levels were not measured. Based on symptoms, multiple organ involvement, and imaging findings, we suspected miliary TB. Sputum and blood smear tests and cultures were negative for TB. Ziehl-Neelsen staining and PCR detected *M. tuberculosis*. Moreover, since a bone marrow biopsy showed acid-fast bacilli, the diagnosis of miliary TB was confirmed, and first-line anti-tuberculosis drugs were initiated. Generally, the patient received 8 doses of etoposide alongside anti-TB treatments. After these efforts, significant improvements were observed in the patient's status and laboratory tests. The patient was stable, organ functions recovered, no evidence of shock, sepsis, or recurrence of disorder was seen and he was receiving supportive care. However, he got asystole suddenly for an unknown reason. Despite performing CPR, our

ultimate efforts were not effective and the patient passed away.

In 2020, Trovik *et al.* reported a 54-year-old male who had nausea, anorexia, diarrhea, frequent micturition, dyspnea, persistent fever, increased C-reactive protein (CRP) levels, and elevated liver transaminases [12]. They recommended broad-spectrum antibiotics to eliminate probable infections. Differential diagnosis and precise evaluations ruled in the possibility of HLH secondary to miliary TB. They initiated etoposide 75 mg and first-line anti-TB drugs. Symptoms improved and the patient was successfully treated [12]. In 2015, Padhi *et al.* reported the case of a 17-year-old man who was hospitalized with persistent fever, cough, worsening breathlessness, hypoxemia, scleral icterus, lymphadenopathy, and hepatosplenomegaly [13]. He also had microcytic anemia. On subsequent testing, microbiological and serological tests for several pathogens were negative, and blood and sputum cultures and BAL were negative. Bone marrow aspiration and smear revealed tuberculosis and hemophagocytosis suggesting miliary TB and HLH. The patient was given anti-TB drugs and responded well. Many other cases with similar conditions were reviewed by Padhi *et al.* in 2015 [13]. They concluded that tuberculosis should be suspected in patients with mentioned nonspecific findings and that early administration of anti-TB drugs can reduce morbidity and mortality.

The timely diagnosis of miliary TB and HLH has major importance and delays can lead to harmful consequences. Since symptoms and signs of HLH and miliary TB resemble various other conditions, and HLH is also a scarce complication, physicians may encounter some challenges in timely diagnoses of the diseases [1,2,5,7]. In the HLH-2004 trial, diagnostic criteria were defined to help physicians diagnose HLH with more certainty (Table 1). Because of the life-threatening nature of HLH, it is important to consider HLH for conditions such as infections, malignancies, rheumatologic disorders, and immune system deficiency syndromes, and then start the treatment as soon as possible if HLH is suspected rather than waiting for the criteria to be met. The use of glucocorticoids may have good results in the treatment of miliary TB in patients with histiocytic phagocytosis syndrome. However, suppression of the immune system to treat HLH in the case of miliary TB is one of the most challenging issues.

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