

# Primary Hemophagocytic Lymphohistocytosis in Adult Woman; a Case Report

Mohammed Saad Alqahtani, MD

Department of medicine, Collage of medicine, Prince Sattam Bin Abdulaziz University. Alkharj city.

## Abstract

*Hemophagocytic lymphohistocytosis (HLH) is a frequently fatal immune dysregulation disorder. We are reporting a case of HLH in a 37-year old Pakistani female nurse who presented to the emergency department with fever and huge hepatosplenomegaly. Investigations showed cytopenias affecting WBCs and platelets, high ferritin, and positive hemophagocytosis in bone marrow biopsy. The primary designation of HLH was established after ruling out secondary causes including infections, malignancy, rheumatologic disorders, and organ transplants. The case was responding well to the standard immunochemotherapy for HLH without relapsing fevers or the need for bone marrow transplantation.*

**Keywords:** Lymphohistocytosis, Hemophagocytic, Adult, Saudi, Pakistan

## I. INTRODUCTION

Hemophagocytic lymphohistocytosis (HLH) is a rare disorder characterized by immune dysregulation, hyperinflammatory response, and aggressive proliferation of histiocytes that phagocytose normal hematopoietic cells [1]. Primary (familial) HLH is a heterogeneous autosomal recessive disorder while secondary (acquired) HLH occurs after conditions that cause strong immunologic activation, such as infections, malignancies, and rheumatologic disorders, and organ transplants [2, 3]. The annual incidence of primary HLH was estimated at 0.15 per 100,000 children in Sweden [4] and the prevalence was estimated at 1.0 per 100,000 population of different races in the US [5]. However, HLH is probably under-diagnosed and the diagnosis is usually delayed due to non-specific presentation [3, 6]. Untreated HLH is almost always fatal [2]. Even with treatment, the disease has high mortality profile (46% death in the first 3 years), with the majority of deaths occur in the first few weeks [7]. Additionally, two thirds of those who survive needs bone marrow transplantation (BMT) [7]. We are reporting here the diagnosis and the management of HLH in adult expatriate female working in Saudi Arabia.

## II. CASE REPORT

A 37-year old Pakistani female nurse presented to the emergency department at April 2016 complaining of fever for 3 weak with abdominal pain and distention. The fever was around 39 C° and not

responding to antipyretics. The abdominal pain was generalized but more in the right upper quadrant. Additionally, the patient reported having few epoxides of epistaxis of moderate amount but without history of hematemesis or melena. After interrogation, the patient declined any history of exposure to infected patients, exposure to animals, recent travel, or eating raw meat or unpasteurized milk. The patient had no history of weight loss, cough, or night sweat. The patient had no history of joint pain, rash, dry eye, or dry mouth. The patient had history of abortion 4 years ago but no previous surgeries. The patient had no family history of similar complaints, tuberculosis, or malignancy. The parents were relatives.

On examination, the patient was pale without cyanosis or jaundice. The patient had mild fever (oral temperature 38.0 C°) and the rest of vital signs were normal. Cardio-respiratory examination was unremarkable. Abdominal examination showed a markedly distended abdomen with enlarged palpable liver and spleen, 20 cm and 22 cm below the costal margin, respectively. There were no palpable lymph nodes.

Abdominal ultrasound confirmed the hepatosplenomegaly, with no focal lesions. Additionally, there were mild ascites and a small reactive lymph node at the peri-pancreatic region. Abdominal CT showed homogeneously enlarged liver (24 cm) and multi-focal enlarged spleen (16 cm). The patient had multiple large necrotic abdominal lymph nodes in the mesentery, porta-hepatis, aorto-caval, and retro peritoneum. Additionally, the patient had anterior abdominal wall hernia with no bowel obstruction and a large amount of ascetic fluid in the abdomen and pelvis. Chest CT showed multiple indeterminate lung nodules, enlarged right cardio-phrenic lymph nodes, and dilated main pulmonary artery consistent with pulmonary arterial hypertension.

Laboratory examination showed cytopenia with low white blood cells (WBC,  $1.4 \times 10^3/\text{ml}$ ) including neutrophil ( $1.0 \times 10^3/\text{ml}$ ) and lymphocytes ( $3.0 \times 10^3/\text{ml}$ ) and low platelet count ( $84.0 \times 10^3/\text{ml}$ ). Red blood cells count was normal ( $5.0 \times 10^3/\text{ml}$ ) but with high reticulocytes percentage (2.26%), low hemoglobin (140 gm/L), and high ferritin (1725 ng/ml). Liver function tests were impaired with moderately high aspartate transaminase (AST) and alkaline phosphatase. Renal function, blood glucose,

electrolytes were all normal. Bone marrow biopsy showed cellular bone marrow with active trilineage hematopoiesis and increased histiocytes with prominent hemophagocytic activity. Spleen biopsy showed necrotizing granulomatous inflammation. Abdominal lymph node biopsy was planned but was not done due to safety issues. Antinuclear antibodies (ANAs) was positive but all other laboratory evaluation of rheumatic diseases were negative including antineutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin, anti-DNA, anti-Smith (anti-Sm), anti-Sjögren's-syndrome-related antigen A (anti-SSA) and B (anti-SSB), and complements C3 and C4. Multiple blood and urine culture were negative. Acid-fast bacilli (AFB) smear test was negative for tuberculosis. Periodic acid-Schiff (PAS) and Grocott Methenamine Silver Stain (GMS) were negative for fungal infections.

The diagnosis and management plans were discussed amongst physicians from infectious disease, hematology, and rheumatology departments. A diagnosis of HLH, probably secondary to tuberculosis was suggested. Although the AFB smear test was negative, the multiple indeterminate lung nodules and the splenic necrotizing granulomatous inflammation let the team decided to start a short intensive course of anti-tuberculous treatment while waiting for the results AFB culture. The course included isoniazide 300 mg, ethambutol 1200 mg, pyrazinamide 1500 mg, and moxifloxacin 400 mg. The patient condition did not improve 6-weeks after starting the anti-tuberculous treatment. Additionally, the results of AFB culture came negative while weekly laboratory tests and repeated bone biopsy reconfirmed the previous results. The patient was started on standard 8-week HLH treatment protocol including dexamethasone, etoposide, and cyclosporine. Dexamethasone was given 10 mg/m<sup>2</sup> body surface area for the first 2 weeks then tapered into half dose every 2 weeks till reached 1.25 mg/m<sup>2</sup> body surface area for the last 2 weeks. Etoposide doses of 150 mg/m<sup>2</sup> body surface area were initiated twice weekly during the first 2 weeks, then weekly thereafter. Cyclosporin was initiated and maintained on a dose of 6 mg/kg (given orally twice daily). Additionally bacterium and fluconazole were given prophylactically. The patient clinical condition improved after initiation of treatment with no fever. WBC (4.3 x10<sup>3</sup>/ml) and platelet count (126.0 x10<sup>3</sup>/ml) improved in next four months.

### **III. DISCUSSION**

We are reporting a rare case of primary HLH in an adult female. Although the vast majority of primary HLH are presented in childhood, few cases have been reported to start the symptoms in adulthood [8, 9]. For example, two siblings with perforin mutations were diagnosed with primary HLH at age 21 and 22 in Italy [8] and another case with the same mutation was diagnosed with primary

HLH at age 62 years in Japan [9]. Actually, the majority of adult-onset HLH is acquired secondary to triggers. For example, a review of 73 cases of adult-onset HLH diagnosed over 12 years in the US revealed that only 18% were idiopathic while the rest was caused by infections (41%), malignancies (29%), autoimmune disorders (7%), post solid organ transplantation (3%), and primary immunodeficiency (1%) [10]. Additionally, a review of 30 cases of HLH aged 14 to 55 years who received allogeneic hematopoietic stem-cell transplantation in China showed that 27% of them were primary or the underlying disease is unknown [11].

The diagnosis of our case was established using the 2004 HLH diagnostic criteria that required fulfilling 5 out of 8 criteria [12]. In our case, the 5 criteria met were fever, splenomegaly, cytopenias affecting both WBCs and platelets, high ferritin, and positive hemophagocytosis in bone marrow biopsy. The primary designation of HLH in our case was established after ruling out secondary causes including infections, malignancy, rheumatologic disorders, and organ transplants. The case was responding well to the standard immunochemotherapy for HLH [7]. As expected, the final diagnosis and consequently initiation of therapy was relatively delayed due to the non-specific presentation and the time needed to do the investigations and rule out secondary causes [3, 6]. The initial start of anti-tuberculous therapy was decided in the lack of definitive evidence of TB due to the suggestive non-specific findings in the lung and spleen, the possibility of occupational exposure, and the more frequent contribution of infection to HLH among adults of Asian descent [13].

In Saudi Arabia where consanguinity is very common, HLH were reported in few children cases and the majority had the primary type [14, 15]. To the best of our knowledge, the current case is the first HLH diagnosis among adults in Saudi Arabia and the first reported case among expatriate working in Saudi Arabia. Therefore, the current case highlights the critical importance of high degree of suspicion of HLH diagnosis not only in children but also in adults. Additionally, it highlights the critical importance of early and aggressive standard immunochemotherapy which can be life-saving without the need for BMT.

In conclusion, we are reporting a rare case of primary HLH in an adult female who responded well to the standard immunochemotherapy of HLH.

#### **Consent**

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the journal's Editor-in-Chief.

### **Declarations**

### **Competing interests**

The author declare that they have no competing interests.

### **Authors' contributions**

Author made the diagnosis and managed the patient.  
Author read and approved the final manuscript.

### **REFERENCES**

- [1] Allen CE, McClain KL: Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2015, 2015:177-182.
- [2] Mehta RS, Smith RE: Hemophagocytic lymphohistiocytosis (HLH): a review of literature. *Med Oncol* 2013, 30(4):740.
- [3] George MR: Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med* 2014, 5:69-86.
- [4] Meeths M, Horne A, Sabel M, Bryceson YT, Henter JI: Incidence and clinical presentation of primary hemophagocytic lymphohistiocytosis in Sweden. *Pediatr Blood Cancer* 2015, 62(2):346-352.
- [5] Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL: Hemophagocytic lymphohistiocytosis in Texas: observations on ethnicity and race. *Pediatr Blood Cancer* 2010, 54(3):424-428.
- [6] Akenroye AT, Madan N, Mohammadi F, Leider J: Hemophagocytic Lymphohistiocytosis mimics many common conditions: case series and review of literature. *Eur Ann Allergy Clin Immunol* 2017, 49(1):31-41.
- [7] Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, Gardner H, Imashuku S, Komp D, Ladisch S et al: Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002, 100(7):2367-2373.
- [8] Clementi R, Emmi L, Maccario R, Liotta F, Moretta L, Danesino C, Arico M: Adult onset and atypical presentation of hemophagocytic lymphohistiocytosis in siblings carrying PRF1 mutations. *Blood* 2002, 100(6):2266-2267.
- [9] Nagafuji K, Nonami A, Kumano T, Kikushige Y, Yoshimoto G, Takenaka K, Shimoda K, Ohga S, Yasukawa M, Horiuchi H et al: Perforin gene mutations in adult-onset hemophagocytic lymphohistiocytosis. *Haematologica* 2007, 92(7):978-981.
- [10] Otrrock ZK, Eby CS: Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol* 2015, 90(3):220-224.
- [11] Fu L, Wang J, Wei N, Wu L, Wang Y, Huang W, Zhang J, Liu J, Wang Z: Allogeneic hematopoietic stem-cell transplantation for adult and adolescent hemophagocytic lymphohistiocytosis: a single center analysis. *Int J Hematol* 2016, 104(5):628-635.
- [12] Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J et al: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007, 48(2):124-131.
- [13] Rajagopala S, Singh N: Diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics: systematic review from the Indian subcontinent. *Acta Med Acad* 2012, 41(2):161-174.
- [14] Abbaker AI, Dammas AS: Familial hemophagocytic lymphohistiocytosis in two Saudi siblings. *Sudan J Paediatr* 2015, 15(1):57-60.
- [15] Elyamany G, Alzahrani A, Elfaraidi H, Alsuhaibani O, Othman N, Al Mussaed E, Alabbas F: Hemophagocytic Lymphohistiocytosis: Single-Center Series of 12 Cases from Saudi Arabia. *Clin Med Insights Pediatr* 2016, 10:21-26.