Received: 2 December 2020 | Revised: 6 February 2021 | Accepted: 22 February 2021

DOI: 10.1002/ccr3.4033

CASE REPORT

Clinical Case Reports Open Access WILEY

# Hemophagocytic lymphohistiocytosis presented with fever of unknown origin: A case study and literature review

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**Abstract**

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening clinical syndrome, which may present with FUO. The possible diagnosis of HLH must be considered in the differential diagnosis when a patient presents with FUO.

**KEYWORDS**

fever of unknown origin, hemophagocytic lymphohistiocytosis

## 1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome characterized by intense immune and inflammatory system activity. This report presents an adult case with idiopathic HLH and fever of unknown origin (FUO) from Iran. We also review the manifestations, treatments, and outcomes on reports of patients with HLH presenting with FUO.

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening clinical syndrome characterized by the excessive activity of the immune and inflammatory systems.[1] The prognosis of this disease is poor. Studies have reported a mortality rate of 50% to 70%, disregarding etiology.[2,3] While HLH affects mostly infants from birth to 18 months, it has been observed even among adults of different age groups.[4]

The etiology of HLH may be primary or secondary.[5] In the primary or familial type of HLH, genetic mutations disrupt the function of immune cells, such as cytotoxic T cells and natural killer (NK) cells and symptoms usually appear in childhood.[6,7] Secondary or acquired HLH, commonly reported in adults, can be secondary to a variety of diseases including infectious diseases (such as EBV, CMV, HIV, and tuberculosis), malignancies (lymphoma and leukemia), autoimmune diseases (SLE, MS), or rheumatic diseases, all of which cause severe phagocytic activation and impaired immune regulation.[8,9]

Most patients with HLH present with acute involvement of various organs. Typical findings include lymphadenopathy, neurological symptoms, pancytopenia, organomegaly, and fever.[7,10] Although fever is one of the most common manifestations of HLH, long-term fever without a known cause has been reported less frequently.[10]

Fever of unknown origin (FUO) is characterized as a disease with a fever above 38.3°c that lasts for at least three weeks; sometimes, no specific cause can be found despite diagnostic tests and evaluations.[11] Common etiologies include

infections, malignancies, and rheumatic diseases.[12,13] The presentation of HLH with FUO has been reported in a few case reports. Here, the clinical course of an adult case with FUO eventually diagnosed with HLH is reported; a comprehensive review is conducted, emphasizing the manifestations, treatments, and outcomes on reports of patients with HLH presenting with FUO. Written informed consent was obtained from the patient.

## 2 | CASE PRESENTATION

A 70-year-old man was referred to the hospital with prolonged fever. He reported fever that he had for the past two months. At the time of admission, his body temperature was 39°c. Other vital signs included blood pressure, 130/85 mm Hg; respiratory rate, 19; and pulse rate, 93 beats per minute. The patient had no pulmonary or urinary symptoms. Further, the physical examination did not reveal any lymphadenopathy and was unremarkable. Laboratory data showed a white cell count of 13 500 cell/μL, hemoglobin 8.2 g/dL, and platelet 73 000 cells/μL.

Further testing revealed erythrocyte sedimentation rate (ESR) of 86 mm/h, C-reactive protein of 17 mg/L, ferritin level of 670 ng/mL, triglyceride of 281 mg/dL, and fibrinogen level of 120 mg/dL. He also had transaminases with aspartate transaminase (AST), 78; alanine transaminase (ALT), 90; and alkaline phosphatase (ALP), 1468. Due to the patient's persistent fever, more laboratory tests for FUO were performed. It included Wright, HIV antibody 1 and 2, CMV-IgM Ab, and EBV-VCA IgM Ab all of which reported negative results. Blood cultures were negative on two separate samples. Also, no evidence was observed in favor of vegetation in echocardiography. Abdominopelvic CT scan revealed splenomegaly. Chest CT scan was normal. Due to fever, bi-cytopenia, and high ESR level, bone marrow biopsy and aspiration were performed. The bone marrow examination was reported normal. According to high ALP, the MRCP was performed for the patient and the result was normal. Endoscopy and colonoscopy were also normal. We performed lumbar puncture, and the cerebrospinal fluid had normal analysis. Autoimmune panel was checked and was all negative. Due to FUO and lack of diagnostic results for the patient, liver biopsy was performed which revealed nonspecific inflammatory findings. Finally, by excluding other causes, as well as according to the clinical findings and laboratory data that met the 2004 HLH-diagnostic criteria, the diagnosis of idiopathic HLH was provided (Table 1). High index of suspicion is required for diagnosis as delay increases mortality. The patient was treated with etoposide and dexamethasone. No evidence of recurrence was found at his 5-month follow-up. The patient tolerated the regimen well.

**TABLE 1** HLH-2004 Diagnostic Criteria and Patient's Clinical Finding

| HLH-2004 diagnostic criteria | Patient's initial clinical findings |
|---|---|
| Fever | Present |
| Splenomegaly | Present |
| Cytopenia (≥2 of 3 lineages) | |
| Hemoglobin < 9 g/dL | 8.2 g/dL |
| Neutrophil < $1 \times 10^9$ cells/L | 10 800/$mm^3$ |
| Platelet < $100 \times 10^9$ cells/L | 73 000/$mm^3$ |
| Hypertriglyceridemia or hypofibrinogenemia | |
| Fasting triglyceride ≥ 265 mg/dL | 281 ng/mL |
| Fibrinogen < 1.5 g/L | 1.2 g/L |
| Low NK cell activity | Not performed |
| Ferritin ≥ 500 ng/mL | 670 ng/mL |
| Soluble IL-2 ≥ 2400 U/mL | Not performed |
| Hemophagocytosis in bone marrow, spleen, or lymph nodes | No hemophagocytosis |

## 3 | DISCUSSION

A total of 24 case reports diagnosed with HLH presenting with FUO between 2009 and 2020 were reviewed.[5,14-34] Table 2 provides more details of the covered reports, including treatment regimens, other symptoms, and outcomes. Distributions of reported cases in the world are shown in Figure 1. Geographically, most reported cases were related to China and the United States. Patients aged from 8 weeks to 78 years. The probable etiology of HLH was as follows: tuberculosis (n = 10, 32%), EBV infection (n = 4, 13%), idiopathic (n = 4, 13%), lymphoma (n = 3, 9.6%), Leishmaniasis (n = 2, 6.4%), and HIV infection (n = 2, 6.4%); other etiologies, including staphylococcal infection, CMV, chronic granulomatous disease, and arthritis, were each reported in one patient. Corticosteroids were the most commonly prescribed drug in the course of treatment. Other treatments, such as etoposide, cyclosporine, and IVIG, were used as either monotherapy or in combination depending on the patient's condition. Finally, the mortality rate in these patients was as high as 29%.

A major pathogenic feature of HLH is abnormal immune activation, whether in primary or secondary HLH, in which excessive inflammation causes tissue damage. Immune dysregulation is assumed to be closely related to the abnormal regulation of activated macrophages and lymphocytes. Increased macrophage activity followed by excessive secretion of cytokines in HLH results in cytokine storm, which causes, in turn, severe tissue damage that can lead to organ failure explaining the disease's high mortality rate. On the other hand, NK cells and cytotoxic T lymphocytes cannot eliminate active macrophages, which causes an imbalance in the immune system's regulation.[1,35] As mentioned earlier, a variety of secondary

**TABLE 2** Summary of the case reports included in review

| Year | Publication | Underlying disease | Age (year)/gender | Country | Presenting symptoms | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 2009 | Kerzel et al[23] | EBV | 17/F | Germany | FUO, recurrent diarrhea | IVIG; Corticosteroids; Cyclosporine | Complete remission |
| 2009 | Su et al[19] | Tuberculosis | 58/M | Taiwan | FUO, Hypotension | - | Expired |
| 2010 | Flew et al[21] | HIV | 46/M | United Kingdom | FUO, Hematuria, loin pain | Corticosteroids; Chemotherapy (ABVD) | Complete remission |
| 2010 | Vishwanath et al[20] | Juvenile idiopathic Arthritis | 17/F | India | FUO, arthralgia | Corticosteroids; Cyclosporine | Complete remission |
| 2014 | Khadanga et al[24] | T-Cell NHL | 78/F | United States | FUO, Fatigue, weight loss | Corticosteroids | Complete remission |
| 2014 | Khadanga et al[24] | T-Cell Lymphoma | 69/M | United States | FUO, hepato splenomegaly, pancytopenia | Chemotherapy | Under treatment |
| 2014 | Kuitert PC et al[32] | EBV | 11/M | Netherland | FUO, abdominal pain | Chemotherapy | Complete remission |
| 2014 | Rademacher et al[31] | Idiopathic | 75/F | Germany | FUO, body aches | Corticosteroids | Complete remission |
| 2014 | Rademacher et al[31] | Idiopathic | 16/F | Germany | FUO, rash, body aches | Corticosteroids | Complete remission |
| 2014 | Valentine et al[33] | Chronic granulomatous disease | 8 week/M | United States | FUO, rash | Corticosteroids; Cyclosporine; Anakinra | Partial remission |
| 2015 | Rathnayake et al[25] | Tuberculosis | 40/F | Sri Lanka | FUO, arthralgia, myalgia | Corticosteroids | Complete remission |
| 2015 | Samra et al[27] | Idiopathic | 36/F | United States | FUO, dry cough | Corticosteroids | Complete remission |
| 2016 | Bae et al[17] | Idiopathic | 60/F | South Korea | FUO, AKI | Corticosteroids; etoposide; Cyclosporine | Complete remission |
| 2016 | Bandhani et al[29] | Idiopathic | 48/M | Pakistan | FUO, epigastric pain, weight loss | Corticosteroids; etoposide | Expired |
| 2017 | Zhang et al (case series)[28] | Tuberculosis | 8 case 23-78/F(6)-M(2) | China | FUO | Corticosteroids; cyclosporine (1 case), etoposide (1 case) | Expired (6); complete remission (2) |
| 2018 | Cordes et al[15] | ALK-positive Anaplastic Large Cell Lymphoma | 38/M | United States | FUO, abdominal pain | Chemotherapy (CHOP-E) | unknown |
| 2018 | Saevels et al[26] | EBV | 17/F | Belgium | FUO, lethargy, rash | Corticosteroids; etoposide; IVIG; cyclosporine | Complete remission |
| 2018 | Costa et al[16] | Visceral Leishmaniasis | 32/F | Portugal | FUO, hematemesis, melena | IVIG; Corticosteroids | partial remission |

(Continues)

**TABLE 2** (Continued)

| Year | Publication | Underlying disease | Age (year)/gender | Country | Presenting symptoms | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 2018 | Lutfi et al[30] | EBV | 51/F | United States | FUO, flu-like symptoms | Corticosteroids; etoposide | Treatment failed. Palliative care |
| 2019 | Amisha et al[22] | Staphylococcal UTI | 22/M | India | FUO, chills and rigors | Corticosteroids | Follow-up lost |
| 2019 | Mendez et al[5] | B-cell Lymphoma | 70/M | Spain | FUO, cough, abdominal pain | Corticosteroids; etoposide; IVIG; Chemotherapy (CHOP) | partial remission |
| 2019 | Vanhinsbergh et al[14] | Leishmaniasis | 53/M | United Kingdom | FUO, weight loss, pancytopenia, splenomegaly | Liposomal amphotericin B | Complete remission |
| 2020 | Egge et al[18] | HIV | 33/M | United States | FUO, lymphadenopathy | Anti-retroviral therapy | Follow-up lost |
| 2020 | Hasan et al[34] | CMV | 6/M | Qatar | FUO, weight loss, abdominal pain | Corticosteroids; Cyclosporine; IVIG | Expired |

causes, including infections, malignancies, and autoimmune causes, can trigger the disease and imbalance in the immune system. A systematic review reported that infectious causes were the most common cause of HLH [36]; this was consistent with the reports included in this article, with 20 cases out of 31 patients having an infectious etiology. In many cases, the underlying etiology of HLH is unclear, making it very difficult to diagnose. The diagnosis of HLH is very challenging; it is indeed based on a set of clinical, laboratory, and histopathological findings. According to the HLH-2004 guideline, either MLH-compliant molecular detection or at least five of the eight criteria presented in Table 1 may exist to diagnose HLH. Accordingly, in this study, the patient fulfilled five criteria and was diagnosed with idiopathic HLH. One of the clinical criteria and manifestations is fever, which occurs in more than 90% of patients.[3] Hemophagocytosis in bone marrow biopsy is reported 25 to 100 case and is not necessary for the diagnosis.[37] Secondary or acquired HLH, commonly reported in adults, can be secondary to a variety of diseases including infectious diseases, malignancies, and autoimmune diseases or rheumatic diseases, all of which cause severe phagocytic activation and impaired immune regulation. In patients with the diagnosis of HLH, diagnostic evaluations should be done for identifying the cause.[8,9] However in our case after complete evaluations, no underlying diseases were detected.

According to the present report and other case reports, prolonged fever without a known origin can be the first or only manifestation in patients with HLH.[35] Assessing patient with FUO is often very difficult and challenging.[36] On the other hand, the causes of FUO, like the etiology of HLH, are very similar. Infections, malignancies, and rheumatic diseases are the leading causes of FUO; this makes the diagnosis of the underlying cause of fever complicated, resulting in delays in rapid diagnosis and treatment to prevent unpleasant consequences.[38] According to the HLH-2004 guideline, initial treatment includes eight weeks of treatment with etoposide, corticosteroids (dexamethasone), or cyclosporine. Also, intrathecal therapy may be used in high-risk patients. If the disease is still active after the initial treatment, maintenance therapy will continue for a longer time. Other treatment regimens, such as IVIG or chemotherapy, are also used.[3] In most of the previously reported cases, corticosteroids are used as the first treatment line. IVIG and cyclosporine are usually prescribed in cases of steroid resistance.[6,27] Hence, in this work after consultation with hematologist, it was decided to treat the patient with etoposide and dexamethasone. Regardless of the etiology or clinical manifestations, HLH is associated with a high mortality rate if not treated. In general, the underlying etiology determines the disease prognosis. Death from HLH can be due to multiple organ failure, susceptibility to infection, and bleeding due to cytopenia or related to patient treatments such as chemotherapy. However, many factors including age less than 50 years, shorter time for diagnosis and

**FIGURE 1** Distributions of reported cases of HLH and FUO in the world

treatment initiation, subsidence of fever within three days of diagnosis, lower serum ferritin level, and optimal health status before the diagnosis are favorable prognostic factors.[6,39]

In summary, HLH is a fatal disease particularly challenging to be diagnosed due to its rarity. Highly variable clinical presentations, laboratory findings, and associated diseases make diagnosis more difficult. On the other hand, the identification of the FUO etiology as one of the HLH manifestations and the etiology similarity between FUO and HLH itself makes the diagnosis even more difficult. Often the main problem in starting treatment is delayed diagnosis. Treatment should be based on the patient's underlying health conditions, clinical manifestations, and suspected underlying causes. This study contributes to the literature by comparing and reviewing clinical manifestations and outcomes of patients with HLH.

## ACKNOWLEDGMENTS

Published with written consent of the patient.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

M.M, A.H, and T.GH: acquired data, analyzed, and interpreted the data. A.H and T.GH: assisted in drafting the manuscript. All authors have read, revised, and approved the final manuscript.

## ETHICAL STATEMENT

This research was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (no. IR.SBMU.MSP.REC.1399.592).

## DATA AVAILABILITY STATEMENT

No additional data are available.

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**How to cite this article:** Hakamifard A, Mardani M, Gholipur-Shahraki T. Hemophagocytic lymphohistiocytosis presented with fever of unknown origin: A case study and literature review. *Clin Case Rep*. 2021;9:2350–2355. https://doi.org/10.1002/ccr3.4033