Case Report

# Hemophagocytic lymphohistiocytosis as a diagnostic consideration of fever of unknown origin with pancytopenia and chronic liver disease

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## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a severe disorder of systemic immune dysregulation which can be primary or secondary to autoimmune disorders, malignancy, or infections. We hereby describe a case of a 23-year-old male with severe hepatitis along with pancytopenia and prolonged fever of unknown origin that developed HLH triggered by staphylococcal urinary tract infection. This is a discussion of this unusual disease and its presentation and the diagnostic difficulties which may be encountered in general clinical practice.

**Keywords:** Corticosteroids, hemophagocytic lymphohistiocytosis, Hemophagocytic lymphohistiocytosis-2004 protocol, *Staphylococcus aureus*, urinary tract infection, Widal test

## Introduction

Viral infection especially Epstein—Barr virus (EBV) is the most common trigger for secondary hemophagocytic lymphohistiocytosis (HLH) (29%). Studies have suggested infections, such as *Mycobacterium*, *Plasmodium*, hepatitis E, kala azar, malaria, Leptospira, etc., associated with HLH in tropics.[1] But staphylococcal urinary tract infection (UTI) as a cause has been less commonly described.[1]

This case illustrates the importance of thorough history taking, early diagnosis, and complete workup of a case of fever along with awareness among healthcare professionals about the pitfalls of commonly used diagnostic tests.

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## Case Presentation

One year back, at the age of 22 years (23 years old now), our patient had his first episode of high-grade fever associated with chills and rigors. He was evaluated in a local hospital where a diagnosis of typhoid was made based on a single Widal titer report (1:80 for both anti-H and anti-O which was below the epidemiologic cut-off for the area- 1:80 for anti-O and 1:160 for anti-H)[2]). No blood culture was done. He was treated with several courses of antibiotics for over 3 months, but his fever continued to occur on and off since then.

He was then evaluated in a tertiary care center where his liver enzymes were found to be elevated. The patient and his family refused further investigations and took a leave against medical advice, resorting to faith healing. The patient's condition worsened, and he developed progressively increasing abdominal



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distension, bilateral pedal edema, and jaundice over the next 6 months. This is when the patient was brought to us.

There was no history of jaundice before the onset of the current illness, no prior blood transfusions, no history of intravenous (IV) drug abuse or multiple sexual partners, joint pains, rash, recurrent oral ulcers, chest complaints, palpitations, any unusual bleeding, and neuropsychiatric complaints. The patient is a nonsmoker and nonalcoholic with no history of similar illness in other family members.

On general survey, the patient was very ill [World Health Organization (WHO) performance status-Grade 3] and wasted with body mass index of 16.8 kg/m$^2$, febrile (102 F), with a blood pressure 128/80 mm of Hg. He had mild pallor, icterus, bilateral pitting pedal edema, and features of atrophic glossitis. On abdominal examination, nontender hepatomegaly (6 cm below right costal margin) and massive splenomegaly (8 cm below left costal margin) with shifting dullness was present. There was stony hard dullness, reduced air entry, and vocal resonance in b/l lung bases. Other organ systems were unremarkable.

On admission, routine laboratory investigations showed – pancytopenia with hyperferritinemia (3354 ng/ml, normal 20–250 ng/ml), deranged liver enzymes, and lipid profile [Table 1]. Urine routine/microscopy showed pus cells 5–6/hpf and urobilinogen. On day 3, urine and blood culture showed growth of methicillin-sensitive *Staphylococcus* after 2 days of incubation. During a repeat in-depth history, the patient admitted to having complaints of a burning micturition and an urge to void multiple times a day in the past which he refused on previous instances. He explained that he was hesitant to disclose this in front of others due to prevailing social stigma.

Patient was then treated with parenteral amoxicillin–clavulanate and gentamicin based on sensitivity pattern, but his condition deteriorated [Table 2]. Extensive workup was done to evaluate for cause of pancytopenia and transaminitis [Table 3]. Ultimately, all the negative investigations into the suspected causes prompted bone marrow biopsy which showed hypocellular marrow for age with erythroid hyperplasia, partial maturation arrest in myeloid series, increased iron stores (Grade 4), and mildly elevated plasma cells. Morphologically examination revealed large histiocytes containing multiple concave nuclei of myeloid series cells, suggestive of hemophagocytosis. Bone marrow culture grew methicillin-sensitive *Staphylococcus aureus*.

**Table 1: A table summarizing the lipid profile findings of the patient**

| Lipid profile | Patient's value | Reference values |
|---|---|---|
| T. Cholesterol | 292 mg/dl | <200 mg/dl |
| S. Triglycerides | 852 mg/dl | <150 mg/dl |
| High-density lipoprotein | 25 mg/dl | 40-60 mg/dl |
| Low-density lipoprotein | 168 mg/dl | 100-129 mg/dl |

A diagnosis of HLH secondary to staphylococcal UTI and bacteremia was made (6 out of 8 criteria fulfilled).[3] Patient's family refused the treatment with HLH 2004 protocol drugs owing to financial restraints. He was then started on oral methylprednisolone 2 mg/kg/day along with antibiotic coverage, packed cells, and platelets transfusion. Over the next 1 week blood counts showed improvement and general condition improved. He was discharged on day 24 on oral steroids. Patient attended the outpatient department after 1 week of discharge. His general condition was found to be better. In spite of all the efforts, the patient was lost to follow-up.

## Discussion

HLH-94 defined five diagnostic criteria [fever, splenomegaly, bicytopenia, hypertriglyceridemia (fasting triglycerides >2 mmol/l) and/or hypofibrinogenemia (fibrinogen <1.5 g/l), and hemophagocytosis]. In HLH-2004 update, three additional criteria were introduced; low/absent NK-cell-activity, hyperferritinemia (>500 μg/l), and high soluble interleukin-2-receptor levels (>2400 U/ml). For diagnosis, five of these eight criteria must be fulfilled.[3] HLH-2004 guidelines recommend etoposide, dexamethasone, cyclosporine A as first-line chemoimmunotherapy agents. But in any case, if this protocol cannot be followed owing to any restraints (financial in ours), initiating corticosteroids alone can prove to be life-saving (as in our case). There has been another similar case report, where corticosteroids alone were given in a 20-year-old female but HLH was secondary to primary EBV infection and not *Staphylococcus*.[4]

Studies have concluded that the Widal test has low sensitivity, specificity, and positive predictive value, but has a good negative predictive value.[5] A positive result should always be confirmed with a blood culture. For practical purposes, a treatment decision must be made on the basis of the results obtained with single acute phase sample (interpreted in accordance with the locally prevalent cut-offs) as the disease management cannot be delayed awaiting convalescent phase sample for paired sera study.[6]

A Belgian study on 220 women by Dr Stefan Heytens showed that almost all the patients with symptoms of lower UTI but negative urine culture actually had an infection.[7] Particularly in men, low bacterial counts are significant clinically, because contamination is uncommon.[8] Hence, studies support the use of empiric antibiotics guided by symptoms (dysuria, frequency, and urgency being highly predictive) even if urine dipstick and culture is negative.[7]

## Conclusion

Primary care physicians should keep a high index of suspicion for HLH as early diagnosis and treatment reduces morbidity and mortality. HLH should be routinely suspected in a patient with unexplained fever with pancytopenia and multiorgan failure.

**Table 2: A table summarizing the laboratory parameters during the course of hospital stay**

| Hemogram | Day 1 | Day 13 | Day 18 | Day 23 | Reference values |
|---|---|---|---|---|---|
| Hb (g/dl) | 12.1 | 8.5 | 8.9 | 9.2 | 13-18 g/dl |
| TLC (cells/cumm) | 2200 | 2230 | 4800 | 4952 | 4000-11 000/cumm |
| DLC (N/L/M) | 78/10/0 | 87.5/9/3.1 | 76/21/2 | 81.5/9.7/8.2 | N40-80/L20-40/M2-10 |
| Platelet count (platelets/ml) | 62000 | 90000 | 110000 | 120000 | 15 0000-40 0000/cumm |
| **Liver function tests** | **Day 1** | **Day 13** | **Day 18** | **Day 23** | **Reference Range** |
| Bilirubin (T) mg/dl | 14.71 | 11.32 | 9.9 | 8.7 | 0.1-1.2 mg/dl |
| Bilirubin (D) mg/dl | 8.61 | 6.72 | 4.5 | 4 | 0.0-0.3 mg/dl |
| SGPT U/L | 137 | 128 | 184 | 178 | <50 U/L |
| SGOT U/L | 186 | 217 | 311 | 219 | <50 U/L |
| ALP IU/ml | 707 | 532 | 861 | 639 | 30-120 U/L |
| GGT U/L | 136 | 555 | 279 | 144 | 0-30 U/L |
| S. Protein g/dl | 3.8 | 4.4 | 4.9 | 5.0 | 6.5-8.5 g/dl |
| S. Albumin g/dl | 1.61 | 1.6 | 2.0 | 2.0 | 3.5-5.5 g/dl |
| S. Globulin g/dl | 2.2 | 2.8 | 2.8 | 2.9 | |
| A: G Ratio | 0.7 | 0.59 | 0.70 | 0.70 | 0.8-2 |

**Table 3: A table summarizing the investigations done and the disease entities excluded while evaluating this patient with pancytopenia and chronic liver disease**

| Diseases excluded | Presentation and investigations for exclusion |
|---|---|
| Visceral leishmaniasis | Negative LD bodies, rk-39 ELISA |
| Dengue | Negative NS1 IgG and IgM antibodies |
| Hepatitis B and C | Negative anti-HBC Ab and HbsAg |
| HIV | Negative anti-HIV Ab |
| Celiac disease | No GI complaints and negative anti-TTG Ab |
| Systemic lupus erythematosus and rheumatoid arthritis | No skin rash, joint complaints, and negative ANA |
| EBV | Negative anti-EBV VCA |
| HSV | Negative serology and no skin lesions |
| Malaria | Negative peripheral blood smears |
| Tuberculosis | Negative sputum, urine and blood AFB, negative tuberculin skin test, and no chest X-ray findings |
| CMV | Negative PP65 |
| Malignancy | Negative blood smear, ascitic tap transudative with normal cytology, negative lymph node biopsy, CT abdomen revealed no signs of malignancy |
| Scrub typhus | Negative Weil-Felix and immunochromatographic tests, no rash |
| Leptospirosis | Negative IgM serology or macro agglutination test |
| Parvo virus B19 | Negative IgM serology |
| Wilson disease | Normal serum ceruloplasmin, negative liver biopsy, and normal slit lamp examination |
| Hemochromatosis | Negative liver biopsy, no other endocrine, or skin symptoms |
| Autoimmune hepatitis | Negative antismooth muscle antibodies, negative liver biopsy |
| Glycogen storage disorders | Negative liver biopsy |

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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