Case Report

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS WITH HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS IN IMMUNOCOMPETENT PATIENT: A CASE REPORT AND REVIEW OF THE LITERATURES

Manju Bansal1, Gopal Singh2, Akshit Gupta3, Dhiraj Kapoor4, Krishan5

1 Assistant Professor Department of Medicine Dr. RPGMC, Kangra at Tanda, H.P.
2 Senior Resident Department of Anesthesia, Dr. RPGMC Kangra at Tanda, H.P.
3 Junior Resident, Department of Medicine, Dr. RPGMC, Kangra at Tanda, H.P.
4 Professor Department of Medicine Dr. RPGMC, Kangra at Tanda, H.P.
5 Junior Resident, Department of Medicine, Dr. RPGMC, Kangra at Tanda, H.P.

Corresponding Author: Manju Bansal

Received: 10-10-2023 / Revised: 13-11-2023 / Accepted: 23-01-2024

Abstract
Hemophagocytic lymphohistiocytosis (HLH) secondary to Histoplasma capsulatum infection is a rare disorder a life-threatening hyperinflammatory syndrome. Here, we present a rare case of disseminated histoplasmosis in a non-HIV patient, whose disease course was complicated by HLH with a full recovery after appropriate therapy. Although cases of patients with human immunodeficiency virus (HIV) infection have been well documented, little study has reported in the setting of HIV seronegative. In this study, we report a case of HLH secondary to histoplasmosis in an immunocompetent patient in a Rural tertiary care hospital Dr. RPGMC Tanda H.P. and review all cases on this situation.

Objective: The objective is to study their epidemiology, clinical characteristics, diagnostic approaches, and therapeutic response. A 31 year-old male presented with fever, fatigue, anorexia, and weight loss. Bone marrow examination suggest fungus organism and hemophagocytosis, and bone marrow culture confirmed Histoplasma capsulatum, as the etiology of HLH. The patient was successfully treated.

Review of Literature: We reviewed a total of the 13 cases (including our patient) of HLH with histoplasmosis in immunocompetent patients. Twelve of the 13 patients are from endemic areas, and nine of the 12 cases are from emerging endemic areas, India and China. Three patients had sojourn history may related to the disease onset. Twelve of the 13 cases fulfilled HLH-2004 criteria. The diagnosis of Histoplasma capsulatum infection was established by histological examination (13 of 13), culture (4 of 13), molecular method (2 of 13), and antigen or serological assays (2 of 13). Amphotericin B, posaconazole, and itraconazole show favorable activity against the fungus, seven patients used specific treatment for HLH. For analysis of outcomes, two of the 13 patients died. Our present case report and literature review show that disseminated Histoplasma capsulatum infection with HLH in the immunocompetent population becomes increasingly common in emerging endemic areas and have high mortality. It is essential for clinicians to be highly skeptical of such disease diagnosis due to the non-typical population and disease presentation. Timely diagnosis and early use of antifungal agents will lead to favorable prognosis.

Keywords: HIV seronegative, immunocompetence, histoplasmosis, hemophagocytic lymphohistiocytosis, liposomal amphotericin B.
Introduction
Histoplasmosis is an infection caused by the fungus Histoplasma capsulatum. This fungus typically lives in humid and acidic soil in endemic areas. Soil enriched with bird or bat excrement promotes the growth and sporulation of Histoplasma. It is a dimorphic fungus that causes histoplasmosis. With a worldwide incidence, epidemic distribution mainly in North America and Latin American countries. Many areas of Asia, including India, Southeast Asia, and China along the Yangtze River, are also endemic. Infection occurs when inhalation of fungal spores or hyphae from the environment soil and the lung is the primary organ of infection. H. capsulatum can disseminate throughout the body in immunocompromised persons who are at least 10 times more likely to develop progressive disseminated histoplasmosis (PDH) than the general population, without timely diagnosis and treatment can lead to fatal illness. In immunocompetent and non-respiratory patients, they are usually clinically silent or mild manifestations, and diagnosis is often so challenging that the rate of underdiagnosis is high. Acquired HLH is associated with systemic infections, malignant diseases, or autoimmune disorders, cases onset mainly in adults. Most cases of HLH secondary to Histoplasma capsulatum infection present in immunocompromised patients and clinicians are vigilant in diagnosing the disease in endemic areas. We present a rare case of an immunocompetent patient who was 31 years old and driver by profession and residing in Dehi, diagnosed as Histoplasma infection and secondary HLH, which was successfully treated by Liposomal Amphotericin B (3mg/kg/day) 150 mg /day for 14 weeks followed by Itraconazole 200 mg BD for next 12 months. A review of literature on this situation is also performed.

Case Presentation
A 31-year-old male was admitted to the medicine department of Tertiary care hospital Dr. RPGMC Tanda H.P. with complaints of intermittent fever associated with fatigue and anorexia for 3 months. He also given h/o loss of 6 kg weight for last 3 months. History of pain abdomen (epigastrum) was there for which he took treatment from private hospital where he was diagnosed with chronic calcified pancreatitis and main pancreatic duct stone for which patient undergone ERCP on 7th FEB 2023 but fever persisted. The patient visited our hospital for persistent fever. On physical examination patient was conscious, cooperative well oriented to time, place and person. His vitals were within normal at the time of presentation. Temp. recorded 101°F, pulse rate of 97 /min, respiratory rate of 18/min, and blood pressure of 98/60 mm of hg and has normal oxygen saturation. He had pallor and hepatosplenomegaly. CVS and Respiratory systems were within normal limit. The laboratory examination indicated pancytopenia at admission: hemoglobin, 8.4 mg/dL; platelet, 90× 10^9 /L; leucocytes, 2.7 × 10^9 /L; neutrophils, 1.4 × 10^9 /L. The C-reactive protein (CRP) level was 35 (normal < 8) mg/L and procalcitonin (PCT) level was 1.23 (normal < 60) pg/ml and the GM (galactomannan) level was not elevated. Epstein–Barr virus, cytomegalovirus, hepatitis virus B and C, COVID-19 and Serological results for human immunodeficiency virus (HIV), HCV, HBS ag, scrub typhus, leptospirosis, brucellosis, enteric fever were negative, chronic malaria and tuberculosis is ruled out. His blood and urine cultures were sterile. We had kept possibility of Pyrexia with Pancytopenia, with pancytopenia. Possibility of HLH syndrome secondary to
(1) Infection: - Leishmaniasis and Tuberculosis.
(2) Hematological malignancy /lymphoma was kept.
To fulfill HLH - (2004) Criteria and to make diagnosis bone marrow aspiration and bone marrow biopsy was done. Bone marrow biopsy revealed hemophagocytosis and negative result for bacterial culture. Hematoxylin and eosin (HE)-stained bone marrow demonstrated oval or
round organisms with amaranth nuclei and capsule-like unstained halos around these organisms observed in the cytoplasm of phagocytes s/o histoplasmosis.

Table 1 shows the results of relevant blood investigations. Chest x rays and Computed tomography (CT) of the chest was normal but the abdominal CT showed hepatosplenomegaly and chronic calcified pancreatitis. Figure 2-4 showing CT finding. 2D Echography normal study with EF 55-60%. Final diagnosis made was Pyrexia with hepatosplenomegaly with pancytopenia: -HLH syndrome secondary to progressive disseminated histoplasmosis. The patient received Liposomal Amphotericin B 3 mg /kg /day for 14 days. Monitoring of RFT and Electrolytes were done regularly. At day 4 after treatment, the body temperature settled and general condition of patient improved, followed by tab. Itraconazole 200 mg twice a day for a total of at least 12 months. During follow up patient was afebrile, had gained weight and regression of hepatospenomaly was there.

Cell count, CRP, and serum ferritin improved substantially after a week. In this case, the patient presented with HLH with fever, splenomegaly, elevated ferritin, hyperfibrinogenemia, blood cell abnormalities, and hemophagocytosis. Although he had no immunocompromised disease and never went to epidemic area instead of that he had invasive fungal infection like progressive disseminated histoplasmosis.

**Table 1: Blood investigations of patient.**

<table>
<thead>
<tr>
<th><strong>Hb</strong></th>
<th>6.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>3200</td>
</tr>
<tr>
<td>RBC</td>
<td>2.48</td>
</tr>
<tr>
<td>PLATELETS</td>
<td>105</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>18.9</td>
</tr>
<tr>
<td>procalcitonin</td>
<td>3</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>370</td>
</tr>
<tr>
<td>Prothrombin time/INR</td>
<td>14/1.2</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Normal</td>
</tr>
<tr>
<td>S.ferritin</td>
<td>1030</td>
</tr>
<tr>
<td>ANA/RA factor</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum urea</td>
<td>53</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.18</td>
</tr>
<tr>
<td>Serum Na+</td>
<td>137</td>
</tr>
<tr>
<td>TG</td>
<td>182</td>
</tr>
<tr>
<td>LFT SGOT/SGPT</td>
<td>34/30</td>
</tr>
</tbody>
</table>
Figure 3: CT Abdomen showing hepatosplenomegaly and pancreatic calcification.

Figure 4: Abdominal CT scan showed splenomegaly and hepatomegaly with pancreatic calcification.

Figure 5: H-E stain of bone marrow puncture images showing these oval or round organisms with amaranth nuclei and capsule-like unstained halos around observed in the cytoplasm of phagocytes and few extracellular. Intensely PASS +VE
LITERATURE OF REVIEW

A total of 90 articles were retrieved from the databases without time limit, including 77 papers in English, 8 in Spanish, and 2 in Chinese. Total of 128 cases has been reported till 2022 all over world. Case report and case series for HLH and histoplasmosis were identified in the five databases (PubMed, Embase, Web of science, China National Knowledge Infrastructure, and Wan fang Data) by using search criteria (“lymph histiocytosis, hemophagocytic” [MeSH Terms] and “Histoplasmosis” [MeSH Terms]). This review of literature identified 13 cases (9.4%), presenting a confirmed HLH with histoplasmosis of intact immunology. 65 of 128 (50.8%) patients were infected with HIV; 20 of 128 (15.6%) had rheumatic disease; 15 of 128 (11.7%) had organ transplant history (14 cases with renal transplant, and one case with heart transplant) and 3 of 128 (2.3%) had hematologic malignancy. In India total of 6 cases has been reported so far. Out of that 4 people were HIV negative and 2 were HIV positive and 7th one is our patient. In Himachal Pradesh HLH secondary to histoplasmosis has not been reported, this is the first case of disseminated histoplasmosis with HLH in immunocompetent patient.
# IIHL: SECONDARY TO HISTOPLASMOSIS (INDIA)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Underlying Disease</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al.</td>
<td>2000</td>
<td>50</td>
<td>None</td>
<td>Splenic Aspirate</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>40</td>
<td>HIV</td>
<td>Bone Marrow Bx</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>Chandra et al.</td>
<td>2012</td>
<td>38</td>
<td>HIV</td>
<td>Not Reported</td>
<td>Ketoconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Mukherjee and basu</td>
<td>2015</td>
<td>52</td>
<td>IMMUNOCOMPETENT</td>
<td>AUTOPSY</td>
<td>AMP B</td>
<td>Died</td>
</tr>
<tr>
<td>Sonavane et al.</td>
<td>2016</td>
<td>43</td>
<td>IMMUNOCOMPETENT</td>
<td>Bone Marrow Biopsy</td>
<td>AMP B / ITRACONAZOLE</td>
<td>Survived</td>
</tr>
<tr>
<td>Karthik bommannan et al.</td>
<td>2017</td>
<td>32</td>
<td>IMMUNOCOMPETENT</td>
<td>Bone Marrow Biopsy</td>
<td>AMP B / ITRACONAZOLE</td>
<td>Survived</td>
</tr>
</tbody>
</table>

**Outcomes:**
- Recovery
- Recovery
- Recovery
- Recovery
- Recovery
- Recovery
- Recovery

**Notes:**
- OUT OF THAT 4 PEOPLE WERE HIV NEGATIVE AND 2 WERE HAVING HIV.
- IN HIMACHAL PRADESH HLH SECONDARY TO HISTOPLASMOSIS HAS NOT BEEN REPORTED YET.
The features of the 12 patients and our case with competent immunology are summarized in the Table 2. Two of them were infants, and the others were all older than 16 years. Among the 13 cases whose sex was mentioned, 10 were male patients, including our patient. Four patients were China born, two of them had a sojourn history in Africa, five patients were India born (including one case of us), three patients were America born, and one patient was Germany born but had a visiting of a bat cave when she had traveling in Thailand 8 months before onset. Three patients had job as cook, blood bank worker, and homemaker; occupations of other seven patients were unknown.

The nonspecific clinical syndrome consists of fever (13 of 13), weight loss (8 of 13), anorexia (5 of 13), fatigue (4 of 13), and cough (4 of 13). Among 13 patients whose laboratory tests were mentioned, significant cytopenia involving at least two cell lines, elevated ferritin, hypertriglyceridemia, elevated LDH, elevated hepatobiliary enzymes, and organomegaly (hepatomegaly, splenomegaly, and lymphadenopathy) are common symptoms. NK cell activity was detected in three study. In the cases reviewed, histological and cytological examinations in bone marrow (10 cases) and colon/liver/lymph node/lung/spleen (three cases) lead to fast diagnosis of Histoplasma capsulatum. The fungal was culture in three cases in bone marrow and one case in blood. The etiology was identified by molecular methods in two patients. Antigen and serological assays of histoplasma capsulatum were less used in clinical practice, only detected in two patients.

All patients are treated with first line systemic antifungal formulation with liposomal amphotericin B, and eight disseminated infection patients received step down to azoles as recommended by the Infectious Diseases Society of America10. Condition was improved in 11 patients after antifungal and HLH-specific treatment.

Discussion

Environmental soil is the reservoir of Histoplasma capsulatum11. Contaminated soil of bird or bat cave, especially that found beside chicken coops or under blackbird roosts, provides a luxuriant condition for mold growth12. Histoplasmosis is endemic worldwide; in our literature review, five cases were from China and four cases were from Africa, and two Chinese patients had a history of sojourn in Africa. This suggests that clinicians need to raise awareness of the diagnosis of Histoplasma capsulatum infection in both areas. From its discovery in the United States, a century ago to now its spread around the world, there are three main reasons: convenient travel and enhanced connectivity increases imported and exported cases of histoplasmosis; climate change and anthropogenic land utilization creates conditions that are more conducive to fungi6 and the HIV pandemic and the widely use of immunosuppressive agents results in more cases of histoplasmosis4. Our case report and literature reviews are of great value in the context of a worldwide epidemic. Furthermore, after retrieving data of literatures from five databases, we found that the HLH with histoplasmosis in immunocompetent patient is extremely rare but had high mortality. Therefore, it is necessary for clinicians to understand and recognize the disease. Given what we already know, histoplasmosis endemic is highly associated with AIDS12.

The HLH-2004 criteria are used for diagnosis. Family history or molecular diagnosis is accord with HLH, or five of these eight criteria must be present (fever, splenomegaly, bicytopenia, hypertriglyceridemia and hypofibrinogenemia, hemophagocytosis, low/absent NK cell activity, hyperferritinemia, and high-soluble interleukin-2 receptor levels)13. In our review of the
literature, 12 patients with disseminated histoplasmosis meet the above five of the eight criteria. The standard diagnosis methods of histoplasmosis include growth of mold in culture and confirmation of yeast on cytopathology or histopathology of clinical specimens. Histoplasmosis mold form requires 6 weeks to grow in culture and may lead to delays in patient treatment. By contrast, histopathology and cytology have faster diagnosis process but lower sensitivity and specificity. Antigen detection represents a valuable diagnostic tool and a useful measure of treatment response. Serum antibodies have limited diagnosis utility for produced 4 to 8 weeks after acute histoplasmosis infection and can yield false-negative and false-positive results. Molecular diagnosis is used for the identification of suspected histoplasma capsulatum isolated from culture and it characterized by rapid turnaround times, less susceptibility to host factors and high sensitivity and specificity.

It is worth noting that 11 patients experienced clinical improvement and survived. Two of these patients had been deteriorating and died. Previous literature reviews suggest that the mortality rate of HIV-infected patients with HLH caused by disseminated histoplasmosis is 10%–44%. H. capsulatum infections as a trigger for secondary HLH are primarily consider in our study, but exon detection of HLH mutated genes, NK cell activity, soluble interleukin-2 receptor (sIL2R), and interferon (IFN)-g should be tested to support our speculation. Unfortunately, we did not verify it further. The presence of other hidden immunodeficiency disorders is also uncertain.

Conclusion:
The purpose of this case report is to give an insight into a case of disseminated histoplasmosis with HLH in an immunocompetent male, a differential to be considered in future in a patient presenting with prolonged fever as infections are an important group of etiologies in the Indian scenario. Histoplasmosis-associated HLH is a life-threatening complication. Early diagnosis and management can be life-saving. It is necessary for clinicians to improve the awareness of disease diagnosis due to atypical population and disease presentation. Timely diagnosis and early use of antifungal agents will lead to favorable prognosis.

References


