RESEARCH PAPER

Disseminated Histoplasmosis Presenting with Cytopenias and Hepatosplenomegaly in an Immunocompetent Adult: A Diagnostic Challenge

Dr. Sheik Arshad Ali[1], Dr. Umashankar R[2], Dr. Aishwarya Lakshmi M V[3], Dr. Razook Fareedh[4], Dr. Saketh Ramineni[5], Dr. Albert Shaji[6], Dr. Juber[7]

[1] Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. ORCID: 0009-0000-0885-2150. Email: Arshad.asd2@gmail.com

[2] Associate Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. Email: smart.uma89@gmail.com

[3] Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. Email: aishwaryavenkat2193@gmail.com

[4] Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. Email: drrazookfareedh@gmail.com

[5] Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. Email: rsaketh1992@gmail.com

[6] Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu. Email: shajialbert1@gmail.com

[7] General Practitioner, Haji Ilyas Health Care Center, Ghosinga, Rajasthan. Email: zuberkhan1461@gmail.com

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ABSTRACT

Background: Disseminated histoplasmosis is classically associated with immunocompromised states; however, it can rarely occur in immunocompetent individuals, where it often presents with nonspecific clinical features and poses a significant diagnostic challenge.

Case Presentation: A 36-year-old previously healthy male presented with high-grade fever for 10 days, productive cough for 8 days, and headache. On evaluation, arterial blood gas analysis revealed hypoxemia (PaO_2 68 mmHg), and the patient required supplemental oxygen support. Initial laboratory investigations demonstrated pancytopenia along with elevated transaminases. Imaging revealed hepatosplenomegaly and diffuse ground-glass opacities in the lungs. An extensive diagnostic workup, including tropical fever panel, blood cultures, viral markers, autoimmune screening, and tuberculosis testing, was negative. In view of persistent cytopenias and unresolved systemic illness, bone marrow examination was performed, which revealed numerous intracellular yeast forms within macrophages, morphologically consistent with Histoplasma capsulatum. Associated hemophagocytosis was noted, suggesting secondary hemophagocytic lymphohistiocytosis (HLH). The patient was treated with liposomal amphotericin B followed by oral itraconazole, resulting in significant clinical improvement.

Conclusion: This case highlights that disseminated histoplasmosis can occur in immunocompetent individuals and may mimic common conditions such as tuberculosis and tropical infections. The presence of pancytopenia, hepatosplenomegaly, hypoxemia, and a negative fever panel should prompt consideration of fungal infections. Early bone marrow evaluation plays a crucial role in establishing the diagnosis and guiding timely management.

Keywords: Histoplasmosis; Pancytopenia; Hepatosplenomegaly; Immunocompetent; Hypoxemia; Bone marrow; Hemophagocytic lymphohistiocytosis.

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Disseminated Histoplasmosis Presenting with Cytopenias and Hepatosplenomegaly in an Immunocompetent Adult: A Diagnostic Challenge

1. Introduction

Histoplasmosis is a systemic fungal infection caused by Histoplasma capsulatum, a thermally dimorphic organism that exists as a mold in the environment and converts to a yeast form in human tissue. The infection is acquired through inhalation of microconidia from soil contaminated with bird or bat droppings. While primary pulmonary infection is common, dissemination occurs when the organism spreads via the reticuloendothelial system, involving organs such as the liver, spleen, bone marrow, and lymph nodes [1,2].

Disseminated histoplasmosis (DH) is classically associated with immunocompromised states, including human immunodeficiency virus (HIV) infection, hematological malignancies, organ transplantation, and prolonged corticosteroid use. In such populations, impaired cell-mediated immunity facilitates widespread fungal proliferation [3]. However, an increasing number of cases have been reported in immunocompetent individuals, suggesting that factors such as high inoculum exposure, host susceptibility, or delayed immune response may contribute to disease progression [4,5].

The clinical presentation of DH is often nonspecific, with features such as fever, weight loss, cytopenias, and hepatosplenomegaly. In endemic regions, these manifestations frequently overlap with more common conditions such as tuberculosis, tropical infections, and hematological malignancies, leading to diagnostic uncertainty and delay in appropriate therapy [2,6].

Pancytopenia is an important manifestation of disseminated histoplasmosis and typically reflects bone marrow involvement. In such cases, routine microbiological investigations may be inconclusive, and bone marrow examination becomes a key diagnostic modality, particularly when initial workup is unrevealing [6,7].

In addition, disseminated histoplasmosis may rarely be associated with secondary hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome characterized by excessive immune activation, elevated ferritin levels, and cytopenias. The coexistence of HLH further complicates the clinical picture and may mimic other severe systemic illnesses [8,9].

We report a case of disseminated histoplasmosis in an immunocompetent adult presenting with high-grade fever, respiratory symptoms, hypoxemia, pancytopenia, and hepatosplenomegaly, in whom extensive initial evaluation was non-diagnostic. The diagnosis was ultimately established on bone marrow examination, highlighting the importance of maintaining a high index of suspicion for fungal infections in cases of unexplained systemic illness.

2. Case Presentation

A 36-year-old previously healthy male presented with a **10-day history of high-grade fever**, associated with **productive cough for 8 days** and **diffuse headache**. The fever was intermittent, high-grade, and associated with chills. There was no history of weight loss, night sweats, hemoptysis, rash, bleeding manifestations, or altered sensorium. He had **no known comorbidities**, including diabetes mellitus, chronic liver disease, chronic kidney disease, malignancy, or immunosuppressive conditions, and was not on corticosteroids or immunosuppressive therapy. There was no significant occupational or environmental exposure history.

On presentation, the patient appeared acutely ill but was conscious and oriented. His vital parameters were stable, with a pulse of 78/min and blood pressure of 128/82 mmHg. Oxygen saturation was initially maintained on room air; however, in view of respiratory symptoms, **arterial blood gas analysis revealed hypoxemia (PaO_2 68 mmHg)**, and the patient required **supplemental oxygen support** early during hospitalization.

Given the combination of fever and respiratory symptoms, an initial working diagnosis of **community-acquired pneumonia or tropical febrile illness** was considered, and the patient was started on empirical antimicrobial therapy along with supportive care.

Baseline laboratory investigations revealed **pancytopenia**, with hemoglobin ranging between 9.4 g/dL, total leukocyte count around 3,150/µL, and platelet count approximately 73,000/µL. Peripheral smear demonstrated **normocytic normochromic anemia** without abnormal cells or blasts. Biochemical parameters showed **elevated transaminases** (AST 131 IU/L, ALT 160 IU/L) with preserved renal function.

Inflammatory markers were significantly elevated, including **C-reactive protein (CRP)** and **serum ferritin (1650 ng/mL)**, along with elevated lactate

dehydrogenase (LDH), suggesting an ongoing systemic inflammatory or infiltrative process.

Radiological evaluation revealed:

- **HRCT chest:** Diffuse **ground-glass opacities**, interlobular septal thickening, and bronchovascular prominence, suggestive of an atypical infectious or inflammatory process
- **CECT abdomen: Hepatomegaly (~19 cm) with splenomegaly**

In view of persistent fever and cytopenias, an extensive diagnostic workup was undertaken. A comprehensive **tropical fever panel**, including dengue, malaria, scrub typhus, leptospirosis, and brucellosis, was negative. Blood cultures showed no growth. Viral markers, including HIV, hepatitis B, hepatitis C, CMV, and EBV, were negative. Autoimmune screening with antinuclear antibody (ANA) was also negative.

Given the clinical context, **tuberculosis was strongly considered**, and investigations including CBNAAT and acid-fast bacilli (AFB) staining were performed, both of which were negative. Despite broad evaluation, the patient continued to have **persistent fever, cytopenias, and systemic symptoms**, without a definitive diagnosis.

At this stage, the constellation of **pancytopenia, hepatosplenomegaly, elevated ferritin, and persistent systemic illness** raised suspicion for **disseminated infection, bone marrow pathology, or a hyperinflammatory syndrome such as hemophagocytic lymphohistiocytosis (HLH)**.

In view of unexplained cytopenias and non-diagnostic workup, a **bone marrow aspiration and biopsy** was performed. Bone marrow examination revealed a **cellular marrow with trilineage hematopoiesis**, along with **prominent histiocytosis and evidence of hemophagocytosis**. Numerous **intracellular encapsulated yeast forms within macrophages**, along with extracellular fungal elements, were identified. These organisms were highlighted by PAS and GMS staining and were morphologically consistent with *Histoplasma capsulatum*. No evidence of hematological malignancy was noted.

These findings established the diagnosis of **disseminated histoplasmosis with secondary hemophagocytic lymphohistiocytosis (HLH)**.

Following confirmation of the diagnosis, the patient was initiated on **liposomal amphotericin B**, which resulted in gradual clinical improvement, including resolution of fever and improvement in respiratory status with decreasing oxygen requirement. The patient was subsequently transitioned to **oral itraconazole (200 mg twice daily)** for maintenance therapy.

He showed sustained clinical improvement and was discharged in stable condition with advice for regular follow-up.

Bone Marrow Examination (Detailed Histopathological Findings)

In view of persistent unexplained pancytopenia and non-diagnostic initial investigations, a **bone marrow aspiration and trephine biopsy** was performed.

Bone Marrow Aspirate

The aspirate smears were **particulate and cellular**.

- **Erythroid series:** Showed **normoblastic maturation**
- **Myeloid series:** Demonstrated orderly maturation with all stages represented and no evidence of maturation arrest
- **Megakaryocytes:** Adequately represented and morphologically unremarkable

Differential count revealed:

- Blasts: 1%
- Promyelocytes: 0%
- Myelocytes: 11%
- Metamyelocytes: 9%
- Neutrophils and band forms: 16%
- Lymphocytes: 8%
- Monocytes: 4%
- Plasma cells: 3%
- Eosinophils: 4%
- Basophils: 0%
- Erythroid precursors: 44%

There was **prominent histiocytosis**, with several macrophages demonstrating **hemophagocytosis**, including ingestion of erythroid cells, leukocytes, and platelets.

Fungal Elements

Numerous **intracellular encapsulated fungal spores** were identified within macrophages, along with extracellular fungal forms in the interstitium.

The organisms were:

- Small-sized yeast forms
- Oval to round in morphology
- Showing features consistent with **intracellular parasitization of histiocytes**

These findings were morphologically consistent with ***Histoplasma capsulatum***.

Trephine Biopsy

The bone marrow biopsy was **cellular**, with preserved architecture.

- Increased histiocytes containing **intracytoplasmic fungal organisms**
- Presence of **extracellular fungal elements**
- No evidence of granulomatous inflammation or malignant infiltration

Special Stains and Immunohistochemistry

- **PAS and GMS stains:** Highlighted intracellular fungal organisms
- **CD34:** No increase in blasts
- **CD3 and CD20:** Showed scattered lymphocytes

Final Interpretation

Features were consistent with: **Disseminated histoplasmosis involving bone marrow with secondary hemophagocytic lymphohistiocytosis (HLH)**

Hospital Course, Treatment, and Outcome

Following confirmation of disseminated histoplasmosis on bone marrow examination, the patient was initiated on **intravenous liposomal amphotericin B** as induction therapy.

During the initial phase of treatment, the patient remained hemodynamically stable and continued to receive **supplemental oxygen support**. Over the subsequent days, a **progressive clinical improvement** was noted. The fever curve showed a gradual decline, with **defervescence occurring within the first week of antifungal therapy**.

Serial laboratory monitoring demonstrated:

- **Downward trend in inflammatory markers**, including C-reactive protein
- Gradual reduction in **serum ferritin levels**
- Improvement in cytopenias, with **rising leukocyte and platelet counts**

In parallel, the patient's respiratory status improved, with **reduction in oxygen requirement** and eventual discontinuation of supplemental oxygen.

The patient completed an appropriate course of **liposomal amphotericin B**, after which he was transitioned to **oral itraconazole (200 mg twice daily)** for maintenance therapy.

The total duration of hospitalization was approximately **three weeks**, during which the patient showed steady clinical recovery without major complications.

Follow-up

On follow-up, the patient remained clinically stable, with:

- No recurrence of fever
- Improved appetite and general well-being
- Sustained improvement in hematological parameters

He was advised to continue oral itraconazole therapy and undergo periodic monitoring of liver function tests and blood counts.

Discussion

Disseminated histoplasmosis (DH) is a systemic fungal infection that predominantly affects immunocompromised individuals; however, its occurrence in immunocompetent hosts is increasingly recognized [4,5]. This case highlights an atypical presentation of DH in an immunocompetent individual, posing a significant diagnostic challenge due to overlapping features with more common conditions such as tuberculosis, tropical infections, and hematological disorders [2,6].

The patient presented with acute febrile illness, respiratory symptoms, hypoxemia, pancytopenia, and hepatosplenomegaly, a constellation that initially favored diagnoses such as severe community-acquired infection, disseminated tuberculosis, or tropical febrile illness. In regions where tuberculosis is endemic, such presentations often lead to empirical therapy; however, in this case, extensive evaluation including CBNAAT, AFB staining, and imaging did not support tuberculosis. Similarly, a comprehensive tropical fever panel and viral workup were negative, effectively ruling out common infectious etiologies [2,6].

One of the key clinical features in this case was pancytopenia, which is an important but often under-recognized manifestation of disseminated histoplasmosis. Bone marrow involvement by *Histoplasma capsulatum* can lead to suppression of hematopoiesis and infiltration of the reticuloendothelial system, resulting in cytopenias [6,7]. In such scenarios, bone marrow examination becomes a critical diagnostic modality, particularly when peripheral investigations are inconclusive [6].

The definitive diagnosis in this case was established on bone marrow examination, which demonstrated numerous intracellular yeast forms within macrophages, morphologically consistent with *Histoplasma capsulatum*. Notably, routine microbiological investigations, including fungal culture and KOH mount, were negative, underscoring the importance of histopathological identification in diagnosing disseminated fungal infections [6,9].

An important and distinguishing aspect of this case is the presence of hemophagocytosis with markedly elevated ferritin levels, suggestive of secondary hemophagocytic lymphohistiocytosis (HLH). HLH is a hyperinflammatory syndrome characterized by excessive immune activation and cytokine release, and it is a recognized but underreported complication of disseminated histoplasmosis [8,10]. The coexistence of HLH can further obscure the diagnosis, as it overlaps with severe infections, malignancies, and autoimmune conditions [8].

The patient's clinical course supports this association, with features including:

- Persistent fever
- Cytopenias
- Elevated ferritin
- Bone marrow hemophagocytosis

Although formal HLH scoring was not performed, the constellation of findings strongly suggested a secondary HLH-like state triggered by disseminated histoplasmosis [8,10].

Radiologically, the presence of ground-glass opacities and interlobular septal thickening on HRCT chest reflects pulmonary involvement, which is consistent with the inhalational route of infection [1,2]. Hepatosplenomegaly further indicates dissemination to the reticuloendothelial system [2].

Treatment of severe disseminated histoplasmosis involves induction therapy with liposomal amphotericin B, followed by oral itraconazole for maintenance, as recommended by current guidelines [3]. In this case, early initiation of antifungal therapy following diagnosis led to clinical improvement, resolution of fever, recovery of cytopenias, and reduction in oxygen requirement, highlighting the importance of timely diagnosis.

This case underscores several important clinical lessons. First, disseminated histoplasmosis should be considered in the differential diagnosis of fever with pancytopenia and hepatosplenomegaly, even in immunocompetent individuals [4]. Second, a negative fever panel and tuberculosis workup should prompt evaluation for less common etiologies, including fungal infections. Third, bone marrow examination remains a key diagnostic tool in cases of unexplained cytopenias. Finally, clinicians should be aware of the potential association between histoplasmosis and secondary HLH, which may further complicate the clinical picture

Conclusion

Disseminated histoplasmosis can present in **immunocompetent individuals** with nonspecific features, closely mimicking more common conditions such as tuberculosis and tropical infections. The presence of **pancytopenia, hepatosplenomegaly, hypoxemia, and persistently negative initial workup** should prompt consideration of **disseminated fungal infections**.

This case highlights the pivotal role of **bone marrow examination** in establishing the diagnosis when routine investigations are inconclusive. Additionally, the coexistence of **hemophagocytosis with elevated inflammatory markers** suggests a possible **secondary HLH-like state**, further complicating the clinical picture.

Early recognition and timely initiation of antifungal therapy are essential for improving outcomes and preventing disease progression.

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Tables

Table 1 : Clinical Course

Day	Clinical Events
Day -10	Onset of high-grade fever
Day -8	Development of cough with sputum

Day 0 (Admission)	Fever + hypoxemia (PaO_2 68 mmHg), oxygen started
Day 1–3	Pancytopenia detected, initial workup initiated
Day 3–5	Fever panel, viral markers, TB workup → Negative
Day 5–7	Imaging: hepatosplenomegaly + lung involvement
Day 7–10	Persistent fever + cytopenia → suspicion of systemic disease
Day 10–12	Bone marrow examination performed
Day 12	Histoplasma identified + hemophagocytosis
Day 12–14	Liposomal Amphotericin B started
Week 2	Fever subsides, inflammatory markers decrease
Week 2–3	Cytopenias improve, oxygen requirement decreases
Week 3	Discharged on oral itraconazole
Follow-up	Clinical recovery maintained

Table 2 : Investigations done to look for fever source

Category	**Test**	**Result**	**Clinical Interpretation**
Viral Infections	HIV	Negative	Confirms immunocompetent status
	HBsAg	Negative	Hepatitis B excluded
	Anti-HCV	Negative	Hepatitis C excluded
	CMV DNA PCR	Negative	CMV infection excluded
	EBV	Negative	EBV infection excluded
Tropical Fever Panel	Dengue NS1 / IgM	Negative	Dengue excluded
	Malaria (Peripheral smear/Antigen)	Negative	Malaria excluded
	Scrub typhus IgM	Negative	Scrub typhus excluded
	Leptospira IgM	Negative	Leptospirosis excluded
	Brucella agglutination	Negative	Brucellosis excluded
	Typhoid (Widal / IgM)	Negative	Enteric fever unlikely
Bacterial Infections	Blood Culture – Aerobic	No growth	No aerobic bacteremia
	Blood Culture – Anaerobic	No growth	No anaerobic bacteremia
	Sputum Culture	No growth	No respiratory bacterial pathogen
	Urine Culture	No growth	No urinary source of infection
Tuberculosis Workup	CBNAAT (GeneXpert MTB/RIF)	MTB not detected	Tuberculosis excluded
	AFB Staining (Bone marrow)	Negative	No acid-fast bacilli detected
Autoimmune Screening	ANA (Immunofluorescence)	Negative	Autoimmune etiology unlikely