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Histoplasmosis-Associated Hemophagocytic Lymphohistiocytosis Presenting as Pyrexia of Unknown Origin With Splenic Masses

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 72-year-old
Final Diagnosis: Histoplasmosis-induced HLH
Symptoms: Pyrexia of unknown origin
Clinical Procedure: —
Specialty: Immunology • Infectious Diseases
Objective: Unusual clinical course

Background: *Histoplasma capsulatum* is a thermally dimorphic fungus capable of causing progressive disseminated histoplasmosis, particularly in immunocompromised hosts. Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome resulting from uncontrolled immune activation. The coexistence of HLH and disseminated histoplasmosis is uncommon and poses significant diagnostic and therapeutic challenges.

Case Report: A 72-year-old immunosuppressed woman with rheumatoid arthritis treated with methotrexate, hydroxychloroquine, and adalimumab presented with a 2-month history of intermittent high-grade fevers, weight loss, fatigue, and left upper quadrant pain. Physical examination revealed pallor, lethargy, and splenomegaly. Laboratory evaluation showed pancytopenia, markedly elevated ferritin, hypertriglyceridemia, and hypofibrinogenemia. Imaging demonstrated splenomegaly with splenic masses, hepatic lesions, and pulmonary nodules. Disseminated histoplasmosis was confirmed by positive urine *Histoplasma* antigen testing, immunodiffusion assays (H and M bands), and tissue biopsy demonstrating intracellular yeast forms consistent with *Histoplasma*. Bone marrow biopsy revealed hypercellularity with histiocytosis and hemophagocytosis. Elevated soluble interleukin-2 receptor levels and decreased natural killer cell activity supported secondary HLH. The patient was treated with liposomal amphotericin B followed by oral itraconazole, resulting in rapid clinical improvement and normalization of inflammatory markers, with radiographic resolution at 12 months. This case is notable for HLH associated with disseminated histoplasmosis presenting with splenic masses, an uncommon finding that can mimic malignancy or other infectious etiologies.

Conclusions: This case underscores the importance of considering HLH in patients with disseminated histoplasmosis presenting with persistent fever, cytopenias, and organomegaly. Early recognition and prompt antifungal therapy are critical for favorable outcomes. Although histoplasmosis can occur in immunocompetent individuals, it more commonly affects immunocompromised hosts, as in this patient, highlighting the need for vigilance in high-risk populations.

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Introduction

Histoplasma capsulatum is an environmentally acquired, thermally dimorphic fungus that causes histoplasmosis, a systemic mycosis of significant clinical concern. While histoplasmosis has a global distribution, it is most reported in North America and Latin America. Endemic regions also include several areas in Asia, particularly India, Southeast Asia, and parts of China along the Yangtze River [1].

Infection occurs primarily through the inhalation of fungal spores or hyphal fragments from contaminated soil. The lungs serve as the initial site of infection. In immunocompromised individuals, *H. capsulatum* can disseminate systemically, resulting in progressive disseminated histoplasmosis (PDH), which can be life-threatening without prompt diagnosis and treatment. Individuals with compromised immunity are at least 10 times more likely to develop PDH than the general population [1,2]. Conversely, infections in immunocompetent individuals are often asymptomatic or present with mild, nonspecific symptoms, leading to frequent underdiagnosis.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome characterized by excessive and uncontrolled activation of immune cells, particularly natural killer cells and cytotoxic T lymphocytes. This results in severe immune dysregulation and potential multiorgan damage [3]. HLH can be classified into familial and acquired forms. Familial HLH (FHL) is an autosomal recessive disorder typically presenting during infancy, whereas acquired HLH generally occurs in adults and is associated with systemic infections, malignancies, or autoimmune conditions [4].

Most reported cases of HLH secondary to *Histoplasma capsulatum* infection occur in immunocompromised patients [5]. As such, clinical awareness is crucial in endemic regions, where missed or delayed diagnoses can have serious consequences.

We report a case of disseminated histoplasmosis complicated by secondary HLH in a patient with rheumatoid arthritis receiving immunosuppressive therapy. She presented with systemic symptoms and laboratory findings suggestive of HLH. Diagnosis was confirmed through microbiological and immunological testing.

The patient was treated successfully using a combination of antifungal therapy and a short course of steroids (dexamethasone). This case underscores the importance of considering histoplasmosis as a potential underlying cause of HLH and highlights the need for early recognition and a multidisciplinary treatment approach.

This case is notable for its atypical presentation with multiple splenic masses, which are uncommon in histoplasmosis and can mimic malignancy or other infiltrative diseases, thereby complicating diagnosis. The emphasis on splenic lesions in the title reflects their diagnostic significance and the challenge they posed in this case.

Case Report

A 72-year-old White woman with a past medical history of hypertension, stage 3b chronic kidney disease, and long-standing rheumatoid arthritis (RA) presented with 2 months of intermittent high-grade fever (38.9 to 39.4°C), associated with chills, rigors, dry cough, anorexia, and unintentional weight loss (5.4 kg) over 1 month. She denied night sweats, chest pain, dyspnea, palpitations, syncope, gastrointestinal symptoms, petechiae, or bleeding from any site.

She reported a dragging sensation in the left upper abdomen, significant fatigue, and generalized weakness that impaired her ability to perform activities of daily living. She required assistance for ambulation and getting out of bed.

She reported recent travel to Illinois to stay with her son, during which time she worked in his backyard and on the farm with exposure to farm soil and possible bird or poultry droppings, which are significant epidemiologic risk factors for *Histoplasma* exposure. She denied other travel or cruise history. She enjoyed gardening and lived on a farm that leases land for cattle. A neighboring farm uses chicken manure as fertilizer.

She had received multiple courses of antibiotics prior to presentation: levofloxacin (10 days), azithromycin (1 week), cefdinir (1 week), and penicillin V (21 days), without significant improvement. Her RA had been well controlled for 20 years with methotrexate and hydroxychloroquine (HCQ) for 15 years, and adalimumab (Humira) was added for the past 5 years. Humira was discontinued 1 month prior to the onset of fever due to insurance issues, and all RA medications were subsequently withheld.

On physical examination, she appeared frail, febrile, and lethargic, although hemodynamically stable. A soft, palpable spleen was noted approximately 8 cm below the left costal margin. There was no lymphadenopathy, and cardiovascular and respiratory examination results were unremarkable.

Laboratory findings revealed pancytopenia: hemoglobin 10 g/dL, WBC 3.3×10^9/L, and platelets initially 92 000/µL, decreasing to 71 000/µL. Liver function tests were deranged (previously normal 6 weeks prior). Autoimmune and rheumatologic workups were negative except for a positive rheumatoid factor. Blood and urine cultures were sterile.

An abdominal computed tomography scan revealed splenomegaly with multiple solid-appearing masses, low-density hepatic

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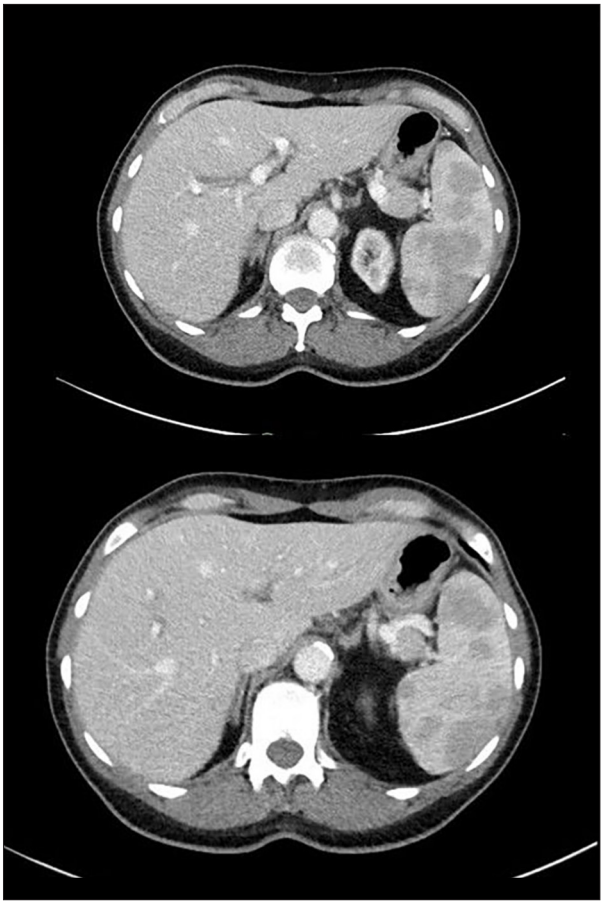

Figure 1. Computed tomography scan showing multiple splenic masses due to histoplasmosis.

lesions, small pulmonary nodules, and right-sided nodular pleural thickening. No lymphadenopathy was present. A CT scan confirmed splenic masses and splenomegaly (**Figure 1**). Central nervous system involvement was ruled out by a brain magnetic resonance imaging (MRI) scan.

Due to the constellation of fever, cytopenia, and splenomegaly, hemophagocytic lymphohistiocytosis (HLH) was strongly suspected. Laboratory markers were significant for: ferritin at 4731 ng/mL, triglycerides at 207 mg/dL, fibrinogen at 137 mg/dL, C-reactive protein at 3.7 mg/dL, erythrocyte sedimentation rate at 15 mm/h, and procalcitonin at 3 ng/mL.

HIV, HBsAg, and HCV test results were negative. A splenic biopsy revealed benign histology with hemorrhage, histiocyte aggregates, and possible fibrosis. Hemophagocytosis was suspected. Cultures and stains (AFB, PAS) were negative.

A comprehensive infectious disease panel was initiated. Serum Fungitell assay was positive twice (210 and 295). Urine antigen testing confirmed *Histoplasma capsulatum*. Immunodiffusion assay reported H and M bands, suggesting active histoplasmosis. *Histoplasma* yeast was identified in the biopsy site. Tests for other fungal and bacterial infections, including *Aspergillus*, were negative.

Peripheral flow cytometry revealed no monoclonal or aberrant lymphocyte populations. Adrenal function was evaluated given incidental adrenal adenoma; serum cortisol was normal (18.3 µg/dL). Echocardiography showed no vegetations.

Despite continued high-grade fever (up to 39.6°C), the patient remained hemodynamically stable. Laboratory testing showed ferritin at 5517 ng/mL, LDH at 461 U/L, triglycerides at 165 mg/dL, fibrinogen at 113 mg/dL, and D-dimer at 3040 ng/mL.

The probability of HLH was further supported by an elevated HScore (a validated clinical scoring system incorporating clinical, laboratory, and cytologic parameters) of 257, corresponding to a greater than 99% likelihood of HLH.

Bone marrow biopsy demonstrated hypercellularity with trilineage hematopoiesis, few hemophagocytic macrophages, and histiocytosis. No blasts or clonal populations were noted. Natural killer cell activity was decreased. Soluble IL-2 receptor (CD25) was markedly elevated to 22 596 U/mL (normal, 137 to 838), fulfilling HLH diagnostic criteria [4]. Disseminated histoplasmosis was confirmed via positive urine antigen, immunodiffusion assays, and tissue identification of yeast forms.

EBV PCR was mildly elevated (373 copies/mL); however, there were no clinical or laboratory findings suggestive of active Epstein-Barr virus (EBV)-driven disease. In the context of confirmed disseminated histoplasmosis, along with the low viral load and absence of supporting features, EBV reactivation was considered unlikely to be the primary driver of HLH in this case.

A diagnosis of HLH secondary to disseminated histoplasmosis was established based on clinical, histological, and laboratory findings. The patient was treated with antifungal therapy (amphotericin B was initiated for 2 weeks, resulting in clinical improvement and resolution of fever; immunosuppressive therapy (dexamethasone (10 mg/m^2/day) was administered for 7 days, then tapered to 5 mg/m^2/day for an additional 7 days per hematology recommendation; and transition therapy (the patient was transitioned to oral itraconazole 200 mg TID for 3 days, followed by 200 mg BID, in which therapeutic levels of 1 to 5 µg/mL were maintained throughout the 12-month course, with dose adjustments as needed).

The patient has remained clinically stable over a 12-month follow-up. Ferritin decreased progressively to 803 ng/mL at 1 month, 409 ng/mL at 3 months, and normalized to 139 ng/mL at 5 months. A repeat CT scan showed resolution of splenic

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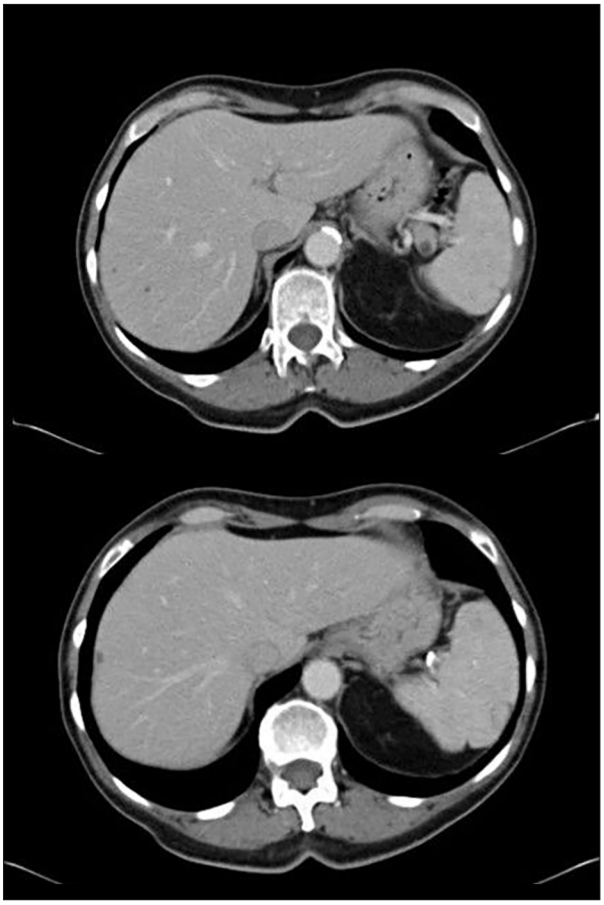

Figure 2. Computes tomography scan showing resolution of splenic masses after treatment for histoplasmosis.

lesions (**Figure 2**). She had rapid clinical and biochemical improvement, without the need for etoposide-based therapy.

She was restarted on hydroxychloroquine (200 mg BID) 12 months into antifungal therapy due to mild RA symptoms. Adalimumab was not resumed. Her symptoms of RA are well controlled with hydroxychloroquine. She is now at her baseline functional status, with stable body weight and no recurrence of fever or systemic symptoms.

Discussion

Histoplasma capsulatum infection is acquired via inhalation of fungal spores, which are subsequently taken up by alveolar macrophages. Within these cells, the organism transitions to its yeast form and replicates intracellularly. In individuals with intact cellular immunity, T-cell-mediated responses activate macrophages, enabling effective clearance of the fungus. As a result, most infections are asymptomatic or subclinical [2].

However, in some cases, *H. capsulatum* disseminates via the bloodstream, with a predilection for organs of the reticuloendothelial system, such as the spleen, liver, bone marrow, and lymph nodes. Disseminated histoplasmosis is primarily seen in individuals with impaired cellular immunity. The highest risk is observed in patients with HIV/AIDS and CD4 counts below 200 cells/μL. Additional risk factors include long-term corticosteroid therapy, solid organ transplantation, and hematologic malignancies [6]. Our patient's history of rheumatoid arthritis treated with methotrexate and adalimumab likely contributed to impaired cellular immunity and susceptibility to dissemination.

In contrast, disseminated disease is rarely seen in immunocompetent individuals and is typically associated with substantial environmental exposure to the fungus. Activities such as cave exploration or soil disturbance in endemic regions have been implicated. Travel to endemic areas, where seroprevalence of *H. capsulatum* is elevated, can be a source of infection even in the absence of overt immunosuppression. While histoplasmosis can occur in immunocompetent individuals, it is more frequently seen in immunocompromised patients, particularly those receiving immunosuppressive therapy, as in our case.

HLH is a severe hyperinflammatory syndrome, most often triggered by malignancies or infections in adults [5]. Among fungal pathogens, *H. capsulatum* has been most linked to HLH. While most cases occur in immunocompromised individuals—particularly those with HIV—other contributing factors include post-transplant states, hematological neoplasms, and immunosuppressive therapies [5].

The combination of HLH and histoplasmosis in immunocompetent individuals is exceptionally rare. There have been 128 documented cases of histoplasmosis-associated hemophagocytic lymphohistiocytosis (HLH), including both HIV-positive and HIV-negative individuals. Notably, only 12 cases have been reported in immunocompetent patients, highlighting the rarity of this condition in individuals without underlying immunosuppression.

Most reported cases involve patients with compromised immune systems, particularly those with HIV infection. In a review of 65 patients, 61% were HIV-positive, and the overall inpatient mortality rate was 31%, with most deaths occurring within 2 weeks of hospital admission [5]. Similarly, other studies have demonstrated that delayed recognition significantly worsens outcomes.

Given the nonspecific clinical features and the overlap between disseminated histoplasmosis and HLH, it is plausible that cases are underreported. Clinicians should maintain a high index of suspicion for HLH in patients presenting with persistent fever, cytopenia, and organomegaly, especially in regions endemic for histoplasmosis.

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Table 1. HLH-2004 Diagnostic Criteria [4].

Diagnosis requires either a confirmed genetic mutation associated with HLH or fulfillment of at least 5 of the following 8 criteria	
Criterion	**Definition**
Fever	Temperature ≥38.5°C
Splenomegaly	Clinically or radiographically identified enlargement
Cytopenias	At least 2 of 3 cell lineages affected: • Hemoglobin <90 g/L • Platelets <100×10^9/L • Neutrophils <1.0×10^9/L
Hypertriglyceridemia/hypofibrinogenemia	Triglycerides ≥265 mg/dL and/or fibrinogen ≤1.5 g/L
Hemophagocytosis	Identified in bone marrow, spleen, or lymph nodes
Reduced or absent NK-cell activity	Documented via functional assay
Hyperferritinemia	Ferritin ≥500 µg/L
Elevated soluble CD25	Soluble IL-2 receptor (sCD25) ≥2400 U/mL

Although EBV is a well-recognized trigger of HLH, its role in this case remains uncertain. The elevated EBV PCR likely represents viral reactivation in the setting of systemic illness and immunosuppression rather than a primary driver of HLH. The identification of disseminated histoplasmosis provides a more plausible underlying trigger in this clinical scenario.

Diagnosing HLH remains a major clinical challenge due to its nonspecific presentation. Symptoms such as persistent fever, pancytopenia, hepatosplenomegaly, and elevated inflammatory markers overlap significantly with manifestations of disseminated fungal infections, particularly histoplasmosis. The HLH-2004 criteria are commonly used to support diagnosis, although they were originally validated in pediatric populations (**Table 1**) [4,7]. Timely recognition is critical, as untreated HLH can lead to rapid clinical deterioration and multiorgan failure.

Management of HLH in adults is complex, and evidence-based guidelines are limited. Treatment hinges on controlling the hyperinflammatory response and eliminating the underlying trigger. In some instances of secondary HLH, resolution can be achieved through effective treatment of the precipitating infection alone. The HLH-2004 protocol—dexamethasone, etoposide, and cyclosporine—is frequently used, although its efficacy in adults, particularly those with secondary HLH, remains uncertain. Intravenous immunoglobulin (IVIG) can also be used adjunctively in select cases. In infection-associated HLH, particularly fungal etiologies, targeted antimicrobial therapy alone can be sufficient in selected cases [3,5].

Therapeutic decisions in disseminated histoplasmosis are guided by disease severity and host immune status. According to the Infectious Diseases Society of America (IDSA) guidelines, a minimum 12-month antifungal regimen is recommended [6]. Itraconazole is the first-line agent for mild to moderate disease, while severe presentations warrant initial treatment with liposomal amphotericin B for 1 to 2 weeks before transitioning to itraconazole.

In the case presented, amphotericin B was chosen as induction therapy due to concern for both disseminated histoplasmosis and HLH. The patient exhibited clinical improvement following antifungal treatment and corticosteroids, without the need for additional HLH-directed therapies. A systematic review involving 65 cases of histoplasmosis-associated HLH found that 23 patients received immunosuppressive treatment for HLH. Amphotericin B was used in 48 patients, whereas azole monotherapy was used in only 5 cases, just 1 of which involved itraconazole alone [8].

The overall prognosis of HLH in adults is poor, with mortality rates approaching 41% [9]. Outcomes are particularly poor when HLH arises from malignancy or remains idiopathic. Mortality associated with histoplasmosis-triggered HLH has been estimated at 31%, increasing to 37% in patients with HIV [8]. In contrast, among the small number of reported cases in immunocompetent hosts, most patients have survived, suggesting a potentially better disease course in this subgroup.

This case highlights the importance of early recognition of HLH in the context of disseminated fungal infections. Given the overlapping clinical features with sepsis, clinicians must maintain a high index of suspicion to avoid delays in diagnosis and treatment [7,10]. This case report adds to the limited literature describing HLH associated with histoplasmosis in immunocompromised patients and highlights the diagnostic challenge posed by overlapping infectious and inflammatory conditions.

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Conclusions

This case highlights a rare but clinically significant presentation of secondary HLH associated with disseminated histoplasmosis in a patient with autoimmune disease and prior immunosuppressive therapy. Prompt recognition and treatment with antifungal and immunomodulatory agents were critical to achieving a favorable outcome. Clinicians should maintain a high index of suspicion for HLH in patients presenting with persistent fever, cytopenia, and organomegaly, especially in endemic regions or those with environmental exposure risks. Early, multidisciplinary intervention is essential to mitigate morbidity and mortality associated with this potentially fatal combination.

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Patient Permission/Consent Declarations

Written and informed consent was obtained from the patient.

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