CASE REPORT

Disseminated Histoplasmosis in a Diabetic Adult: A Case Report and Diagnostic Advances

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ABSTRACT

Histoplasmosis, a fungal infection caused by *Histoplasma capsulatum*, often asymptomatic in healthy people but can cause severe infections in the immunocompromised, leading to progressive disseminated histoplasmosis (PDH). We report a case of a 42-year-old man with a background history of diabetes and chronic hepatitis B infection who presented with gastrointestinal symptoms and leg swelling. Despite initial treatment for septic shock, he did not respond to treatment and developed multiple organ impairments. Laboratory tests showed pancytopenia with negative infectious screening tests. Yeast-like organisms were detected in his blood and bone marrow. A subsequent fungal polymerase chain reaction (PCR) test on trephine biopsy samples confirmed histoplasmosis. This case demonstrates the diagnostic challenges of atypical presentations of histoplasmosis. While traditional detection methods remain crucial, newer techniques such as real-time PCR and next gene sequencing (NGS) offer faster, less invasive options that could improve management. This illustrates the need for clinical adaptation to evolving diagnostic advances in managing such cases.
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INTRODUCTION

Histoplasma capsulatum, a dimorphic fungus endemic to regions with bird and bat droppings enriched soil, generally causes asymptomatic infections in immunocompetent hosts or manifests as flu-like illnesses (1). In immunocompromised individuals, however, it can cause progressive disseminated histoplasmosis (PDH), presenting with non-specific symptoms such as fever, night sweats, and hepatosplenomegaly. This infection may disseminate early, before the immune system responds, but in immunocompetent individual, it often resolves without treatment . In its infective state, Histoplasma capsulatum produces tuberculate macroconidia at room temperature, which facilitates presumptive diagnosis, and the detection of budding yeast at 37°C in tissue or blood cultures confirms the diagnosis (1). This report presents a case of PDH characterised by gastrointestinal symptoms and bone marrow involvement. It also reviews recent advancements in diagnostic methodologies aimed at improving the detection of this complex condition.

CASE REPORT

A 42-year-old man with a history of diabetes and chronic Hepatitis B infection was admitted with a one-month history of loose stools and bilateral leg swelling. Clinical examination revealed tachypnoea, tachycardia, hypotension, significant hepatosplenomegaly and ascites, without fever or jaundice. Despite treatment for suspected septic shock, his condition worsened, leading to scrotal cellulitis. He was started on IV Cefuroxime but remained unresponsive.

Laboratory findings demonstrated progressive pancytopenia, and severe electrolyte imbalances with renal and hepatic impairment. Significant abnormalities observed included hyperuricemia, hyperkalemia, and hyperbilirubinemia, in addition to diminished total protein levels and hypoalbuminemia. Screening for Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), parvovirus B19 and HIV were negative. However, peripheral blood film (PBF) examination during admission demonstrated the presence of intracellular

yeast-like organisms within the monocytes (Figure 1A), requiring a bone marrow aspirate and trephine biopsy examination.

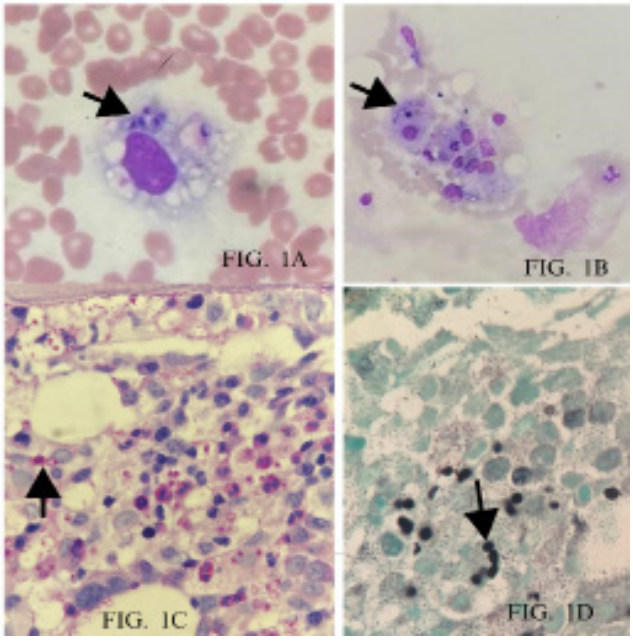

Figure 1 : Figure 1A (PBF x40): Few intracellular yeast-like organisms with eccentric chromatin and pseudo-capsule within monocyte. Figure 1B (BM, MGG x40),1C (Trephine PAS x100),1D (Trephine GMSx100): Histoplasma capsulatum seen within histiocytes as well as extracellularly with eccentric chromatin, clear halo and pseudo-capsule in bone marrow aspirate and trephine biopsy.

Both the bone marrow aspirate and trephine biopsy showed numerous intracellular and extracellular yeast-like organisms, featuring pseudo-capsules and eccentric chromatin within histiocytes (Figure 1B). Additional stains including Periodic acid-Schiff (PAS) and Grocott's Methenamine Stain (GMS), confirmed these findings, showing bright eosinophilic structures and similar morphology, respectively (Figures 1C and 1D).

Given the suspicion of a fungal infection, treatment was intensified with IV Colistin and IV Ampicillin. Real-time PCR analysis of the trephine biopsy confirmed Histoplasma capsulatum, establishing the diagnosis. Plans for liver and renal biopsies were halted as the patient's condition deteriorated. He developed multiple organ dysfunction syndrome (MODS) from severe sepsis and succumbed to the illness.

DISCUSSION

Histoplasmosis, which is caused by the dimorphic fungus *Histoplasma capsulatum*, can exist in yeast form at body temperature or as hyphae in the environment. This fungus is endemic globally and frequently affects immunocompromised individuals, such as the elderly or HIV-infected patients, due to compromised T-cell immunity. Common symptoms include fever, weight loss, cough, chest pain, fever and hepatosplenomegaly. Prompt and accurate diagnosis is crucial given the high risk of severe complications and mortality in immunocompromised patients (1).

In our patient, the presence of yeast-like organisms in monocytes and histiocytes on PBF and bone marrow provided important initial clues, leading to further tests that confirmed the diagnosis of histoplasmosis. Observing such microorganisms in blood films is significant, as they may indicate fungal infections like candidiasis, cryptococcosis, or histoplasmosis, or signal severe systemic conditions such as sepsis.

Our patient's comorbidities likely weakened his immunity, predisposing him to severe histoplasma infection. The complexity of his case, marked by multiple organ impairments and negative results for common pathogens, necessitated definitive diagnostic approaches. Although initial investigations indicated fungal aetiology, their inability to identify specific species highlighted the importance of PCR testing for precise pathogen identification. Cross-reactivity between *Histoplasma* and similar fungi (e.g., *Talaromyces*) can occur microscopically (1). Real-time PCR facilitated rapid species-level confirmation, crucial in this rapidly deteriorating patient, where empirical antifungal treatment had failed.

The gold standard for diagnosing histoplasmosis is culture or yeast identification using special stains, though both have low sensitivity and slow turnaround times, which may take up to two weeks. The Histoplasma antigen (HPA) assay, added to the WHO Essential Diagnostic List in 2018, offers a faster, non-invasive alternative with high sensitivity and specificity (1). The IMMY ALPHA EIA, the most widely used test, detects HPA in urine, serum, or bronchoalveolar fluid, with the highest accuracy in urine especially for PDH. However, false results may occur due to low antigen levels or cross-reactivity. In Malaysia, limited local availability and reliance on overseas testing increase costs and delay results.

PBF is a cost-effective, simple method for detecting Histoplasma yeast cells, aiding in the diagnosis of histoplasmosis. Although less sensitive than antigen testing, PBF remains a reliable method for confirming disseminated histoplasmosis, supporting its use in resource-limited settings to initiate timely treatment while awaiting more definitive results (1). The organisms appear as small (2–4 µm), oval, budding yeasts with a clear halo, typically found intracellularly within monocytes. These features help distinguish them from other fungi like Candida or Cryptococcus. While helpful for early suspicion, PBF has limited sensitivity and cannot definitively confirm PDH.

Antibody detection tests such as he complement fixation test (CFT), immunodiffusion test (ID), and

enzyme-linked immunosorbent assay (ELISA) are useful for diagnosing subacute, chronic, and meningitic histoplasmosis (1). They detect antibodies in serum, plasma, or cerebrospinal fluid, though sensitivity varies with immune status and disease stage. Antibodies may appear weeks after exposure and persist for years, complicating interpretation. Although CFT and ID are considered gold standards, their sensitivity is reduced in immunocompromised or acute cases, while ELISA, though more sensitive, is prone to false positives from cross-reactivity (1).

Molecular approaches like PCR provide high analytical specificity and quicker results compared to traditional diagnostic methods (2). PCR assays targeting sequence-characterised amplified region (SCAR) markers of H. capsulatum enabled the detection of fungal DNA across diverse clinical and environmental samples.

Real-time PCR is a reliable and accurate tool for diagnosing histoplasmosis, offering better sensitivity than earlier PCR methods. It effectively detects infection across various samples, including PDH cases, and is especially useful in non-endemic areas or among travellers. Detection rates from respiratory samples reach 92.8% in disseminated infection and 100% in acute pulmonary cases. In immunocompromised patients with disseminated infection, it detected *H. capsulatum* in 92.3% of blood samples, offering faster results than culture (2). It also aids in post-treatment monitoring and fungal load assessment, although its efficacy may be limited in chronic, non-disseminated histoplasmosis due to low detectable pathogen levels. Real-time PCR shows high sensitivity and specificity in formalin-fixed paraffin-embedded tissue, though its specificity may decrease in co-infections like tuberculosis (1).

While PCR offers rapid and specific detection, its sensitivity may be reduced in low-burden infections or suboptimal samples and limited to detecting only the organisms specifically targeted. Conventional methods, though slower or less specific, may still detect infections in broader clinical contexts where the causative pathogen is not immediately clear.

In recent years, metagenomic next generation sequencing (mNGS) has emerged as a significant advancement in the field, improving the speed and sensitivity of diagnosing fungal infections. It also enhances the study of mycobiomes and fosters the progression of fungal research. This technology accelerates DNA sequencing by analysing fragmented DNA in parallel and assembling genomes using bioinformatics tools (3).

However, its application in histoplasmosis diagnosis is less documented. Chen (4) reported a case where mNGS identified *Histoplasma capsulatum* infection in a young, immunocompetent man from a non-endemic region. Another case involved a young patient with very low CD4, where mNGS of bone marrow confirmed disseminated histoplasmosis within 24 hours by detecting 363 sequences (2.614% of the genome) (3).

NGS shows high detection rates for *H. capsulatum* in blood and bone marrow, and is especially useful for differentiating it from visceral leishmaniasis and *Talaromycosis marneffei,* which share similar clinical and microscopic features (5). These infections occur within mononuclear macrophages and exhibit similar shapes and sizes. NGS's rapid capability to identify multiple organisms in a single run without prior suspicion is especially noteworthy (5).

Despite its advantages, mNGS has notable limitations. It cannot conclusively establish connections between pathogens and diseases and performs less effectively with intracellular bacteria and fungi due to their cell walls, often requiring the sequencing of the human host's genetic background. It is also vulnerable to environmental contamination (3,5). Distinguishing infection from colonisation remains challenging, and the impact on the operational cost can be huge. On the other hand, interpreting NGS results demands specialised expertise and extensive bioinformatics support, while the large data volumes produced by NGS methods complicate effective data management and analysis (3,5).

Recognising the strengths and limits of each diagnostic method is key to diagnosing and managing histoplasmosis. While tools like mNGS and PCR improve accuracy, their cost and technical complexity call for a tailored, resource-sensitive approach.

CONCLUSION

This case highlights the lethality of histoplasmosis infection in immunocompromised patients. PCR testing, which is rapid and specific, plays a key role in addressing the shortcomings of conventional staining methods. While PBF and biopsies are crucial for early suspicion, molecular tools significantly improve diagnostic accuracy, especially in complex cases. Nevertheless, accessibility remains a challenge. Clinicians should maintain high suspicion in high-risk patients and prioritise timely molecular confirmation whenever feasible to reduce mortality in this rapdly progressive infection.

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REFERENCES

1. Toscanini MA, Nusblat AD, Cuestas ML. Diagnosis of histoplasmosis: current status and perspectives. Appl Microbiol Biotechnol. 2021;105(5):1837-59. doi: 10.1007/s00253-021-11159-2.
2. Alanio A, Gits-Muselli M, Lanternier F, Sturny-Leclere A, Benazra M, Hamane S, et al. Evaluation of a New Histoplasma spp. Quantitative RT-PCR Assay. J Mol Diagn. 2021;23(6):698-709. doi: 10.1016/j.jmoldx.2021.02.007.
3. Wang N, Zhao C, Tang C, Wang L. Case Report and Literature Review: Disseminated Histoplasmosis Infection Diagnosed by Metagenomic Next-Generation Sequencing. Infect Drug Resist. 2022; 15:4507-14. doi : 10.2147/idr.s371740
4. Chen J, Li Y, Li Z, Chen G, Liu X, Ding L. Metagenomic next-generation sequencing identified Histoplasma capsulatum in the lung and epiglottis of a Chinese patient: A case report. Int J Infect Dis. 2020; 101:33-7. doi: 10.1016/j.ijid.2020.09.038.
5. Zhang HC, Zhang QR, Ai JW, Cui P, Wu HL, Zhang WH, et al. The role of bone marrow metagenomics next-generation sequencing to differential diagnosis among visceral leishmaniasis, histoplasmosis, and talaromycosis marneffei. Int J Lab Hematol. 2020;42(2):e52-e54. doi : 10.1111/ijlh.13103