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Case Report

Disseminated histoplasmosis leading to end stage liver failure in immunocompetent patient: case report and review of literature.☆,☆☆,★,★★,†,††,†

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ABSTRACT

Histoplasmosis is the fungal infection caused by Histoplasma capsulatum fungus. It is commonly found in a few endemic areas in the United States, where there is a large number of birds or bats and can spread through their droppings. Disseminated histoplasmosis is a severe manifestation of the fungal infection which is commonly seen in individuals with underlying immunosuppression. Our case is an unusual case of disseminated histoplasmosis in a 60-year-old, immunocompetent male patient with a history of significant alcohol abuse, which led to end stage liver failure. While the patient showed some signs of improvement initially upon beginning the treatment, he ultimately continued to deteriorate despite treatment due to an overwhelming histoplasmosis infection. This case demonstrates the importance of keeping a high index of suspicion even amongst immunocompetent patients with no obvious exposure to risk factors. It also shows that timely diagnosis with a high index of suspicion is required with an integrated treatment approach.

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Introduction

Histoplasma capsulatum is found in soil and survives best in areas with large amounts of bird or bat droppings. In the United States, it is most commonly found near the Ohio and Mississippi River valleys [1,2,3]. It is often reported in patients who explore caves and have been exposed to bird or bat droppings [4]. Although patients are usually asymptomatic and the disease is self-limited, some may present due to illness related to infection most commonly pulmonary involvement [1].

One of the more serious forms of the disease, Disseminated Histoplasmosis is a progressive extra pulmonary infection often seen in immunocompromised patients (e.g. AIDS, those on immunosuppressive medications etc.) or at extremes of age [5].

Although the presentation may vary from patient to patient, disseminated histoplasmosis is a life-threatening disease, which requires a high index of suspicion and institution of prompt treatment.

Here we present the case of an immunocompetent patient, with no reported risk factors, suffering from Disseminated Histoplasmosis manifesting with severe hepatic and bone marrow involvement along with circulatory shock.

Case history

A 60-year-old male with past medical history of significant for alcohol abuse presented to clinic with 3 weeks of weakness, fatigue, intermittent fevers, and jaundice. He also noted abdominal pain, nausea, cough, rhinorrhea, and brown-colored urine. The patient is a truck driver from out of state and just passing through the area.

In the clinic, laboratory findings were remarkable for total bilirubin 11.4, alkaline phosphatase (ALP) 598, serum albumin 2.0, Platelet count 64000, and sodium 128. Due to these findings, the patient was directed to the emergency department (ED). In the ED, patient had tachycardia (heart rate of 113) and mean arterial pressure in the mid-60s. The INR was 1.4. On imaging, CT chest, abdomen and pelvis showed an indeterminate cavitary lesion in the lower lobe of the left lung as well as hepatomegaly and an indeterminate intrahepatic lesion. The patient was then admitted to the hospital (Fig. 1).

Gastroenterology and Pulmonology consultations were obtained. The patient's presentation was consistent with cholestatic liver disease and underwent right upper quadrant ultrasound and MRCP (Magnetic resonance cholangiopancreatography) to evaluate for biliary obstruction. These studies showed a normal-sized biliary duct and no sign of obstructing pathology. There were no signs of cirrhosis on MRCP imaging. The patient tested negative for hepatitis B and C and serum alfa fetoprotein (AFP) levels were undetectable. Pulmonology consultant felt the patient's lung lesion was most likely an abscess and that this could be the cause of the patient's consistent fevers. The patient was started on ampicillin-sulbactam antibiotics and underwent CT-guided lung biopsy. Biopsy results eventually returned positive for histoplasmosis (Fig. 2). Infectious disease was consulted and felt that the patient's liver pathology was likely due to disseminated histoplasmosis and started liposomal amphotericin B on hospital day 5.

Despite in-depth history taking, the patient had no known exposures that would put him at risk for histoplasmosis. He lived rurally and did yard work, but other than this, he was not in outdoors often. He had no contact with birds or bats and denied caving. The patient also was not immunocompromised. HIV was tested and returned negative. Occult malignancy was considered, but there were no signs of this on CT chest, abdomen, and pelvis imaging. The only factor identified as a possible immune suppressor was the patient's heavy alcohol use.

Patient's clinical condition worsened. He became increasingly short of breath and was found to have gained 10 lbs since admission. TTE revealed newly diagnosed heart failure with reduced ejection fraction of 31%. The patient was started on scheduled albumin and furosemide. Patient's blood pressure continued to worsen to the point where he was transferred to the intensive care unit (ICU) and started on norepinephrine to maintain adequate perfusion. Scheduled midodrine was started and patient was able to be weaned from pressors and transferred out of the ICU.

The patient initially struggled with severe thrombocytopenia. At its nadir, the patient's platelet count was 5000 and he was requiring platelet transfusions. Hematology and/or Oncology was consulted due to the extent of the patient's thrombocytopenia and concern for possible malignancy that could be suppressing bone marrow production and causing immunosuppression. The patient underwent bone marrow biopsy that showed severe bone marrow infiltration by histoplasmosis, but no other abnormalities.

Liver enzymes worsened as well. About two weeks after admission total bilirubin was 22.8 and Alkaline phosphatase was 1266. After two weeks of liposomal amphotericin B treatment, the patient was transitioned to Itraconazole. Liver enzymes slowly improved during the first few weeks of treatment. About a month after admission, the patient had normal AST and ALT levels (Aspartate transaminase and Alanine transaminase), and serum ALP levels had decreased to 304.

Unfortunately, this trend did not continue, and serum liver tests all began to worsen again. The patient continued to struggle with hypotension. He also began spiking intermittent fevers. The patient underwent paracentesis, was found to have SBP, and received a course of Ceftriaxone. There was concern for possible underlying alcoholic hepatitis in the setting of the patient's alcohol abuse that could be responsible for the patient's failure to improve, thrombocytopenia, and worsening serum liver tests so the patient underwent a CT-guided liver biopsy to evaluate (Fig. 3). This returned with severe histoplasmosis infiltration but no signs of alcoholic hepatitis. The patient remained stable and was discharged to a skilled nursing facility after 6 weeks in the hospital (Table 1).

The patient was readmitted a week later due to hematochezia and worsening hypotension. Ultimately, he was not thought to have a GI bleed, but was thought to be failing histoplasmosis treatment due to increasing liver enzymes (ALT 121, AST 141, ALP 1,919, Albumin 1.6) and cachexia. It was hypothesized that histoplasmosis may have infiltrated the GI tract, affecting absorption of Itraconazole and nutrition in general.

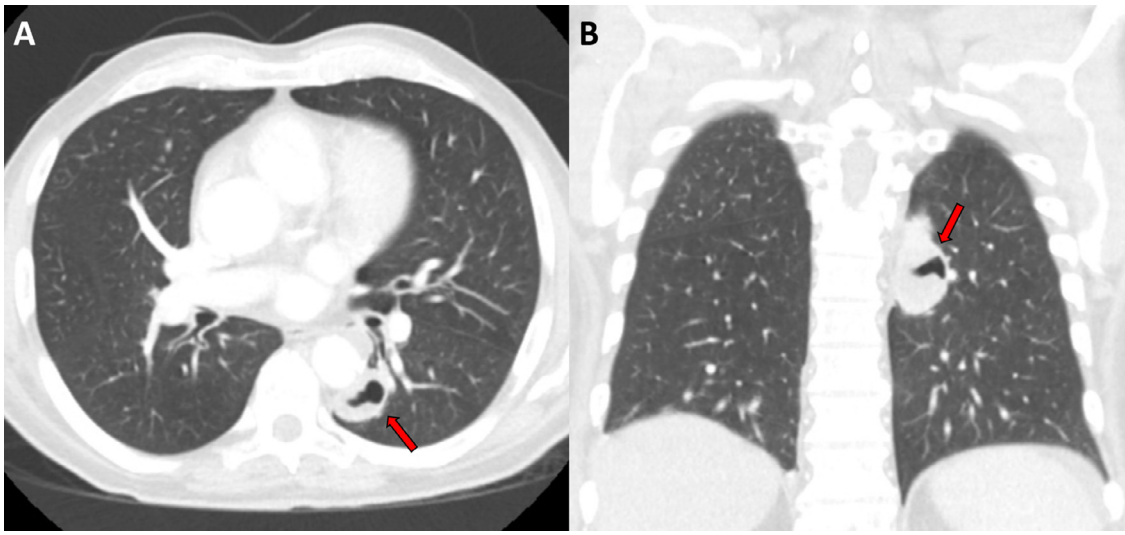

Fig. 1 – Chest CT axial view (A) and coronal view (B) lung window shows well defined thick irregular walled cavitation in superior segment of left lower lobe adjacent to the descending thoracic aorta

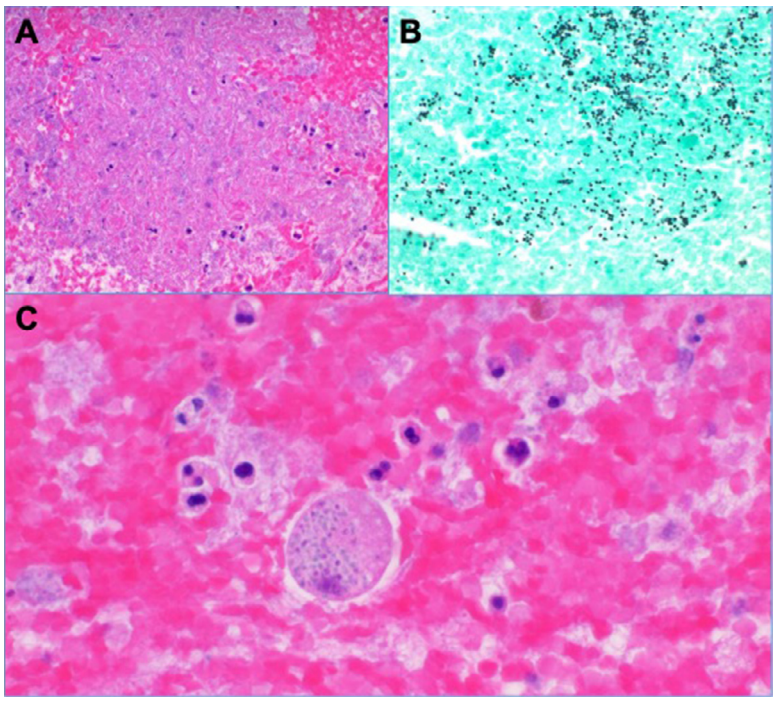

Fig. 2 – Pulmonary involvement by Histoplasma. Lung FNA shows (A) necrotizing granulomatous inflammation (H&E stain, medium power) (B) abundant histoplasma organisms (GMS stain, medium power) and (C) rare organism-laden histiocytes (H&E, high power)

A fecal fat study was abnormal and confirmed malabsorption. This was thought to explain the patient's weight loss and cachexia despite good oral intake. A PICC line was placed and the patient started TPN (Total Parenteral Nutrition) to improve nutrition. Itraconazole was discontinued and the patient was restarted on liposomal Amphotericin B. Despite this, the patient's liver enzymes continued to worsen and both urine and blood histoplasma antigens increased due to overwhelming histoplasmosis infection. The patient was discharged to a long term acute care facility with follow-up arranged with infectious disease. His prognosis is felt to be extremely poor.

Patient was again readmitted within a week with continue to decline health and slow mentation. CSF analysis did not show evidence of histoplasma. Due to his decline health transition to hospice care and passed away 3 months after his initial symptoms started.

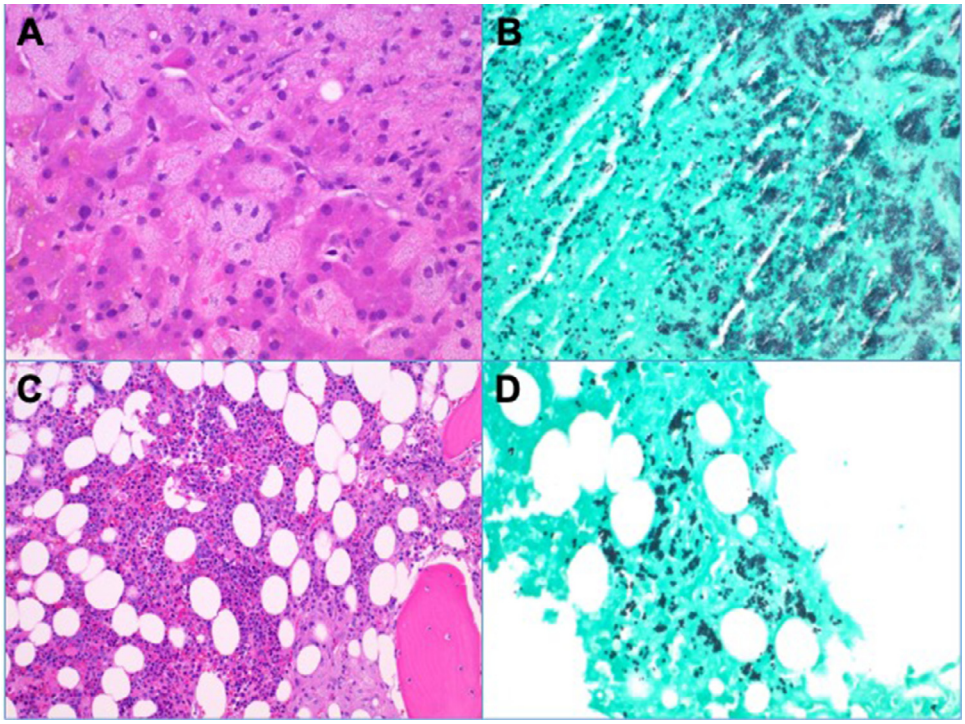

Fig. 3 – Liver and bone marrow involvement by disseminated Histoplasmosis. Liver (A and B) shows numerous sinusoidal macrophages (lower left) and confluent necrosis (upper right) (A- H&E, medium power). GMS stain (B) shows abundant Histoplasma organisms (medium power). Bone marrow (C,D) shows a reactive increase in trilineage hematopoiesis (C) with aggregates of foamy macrophages(lower right) (C, H&E low power) and GMS stain confirmed numerous Histoplasma organisms (D, GMS, medium power)

Table 1 – Weekly liver function tests and platelets

	Reference values	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
AST	8-48 U/L	44	29	114	77	35	79	141	121	156
ALT	7-55 U/L	41	38	142	82	40	58	121	106	111
Alk Phos	40-129 U/L	598	364	1137	846	304	648	1919	1533	1928
T. Bili	0.1-1.2 mg/dL	11.4	15.0	21.7	19.3	20.6	19.7	14.6	14.4	11.9
Albumin	3.5-5.0 g/dL	2.0	2.5	2.0	2.0	2.1	2.0	1.6	1.6	1.4
Platelets	150-450 10^9/L	64	5	11	21	61	77	79	50	48

Discussion

Histoplasmosis is an endemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*. Chicken coops, farms, abandoned buildings, and caves are high-risk areas for infection. Activities that expose people to these settings, such as construction, demolition, spelunking, or cleaning bird droppings or bat guano can put them at risk for infection [1,6].

Upon inhalation of histoplasma conidia, it reaches the lungs where they change to their yeast form, the pathogenic phase causing the disease. It is then phagocytosed by the macrophages. Inside the macrophages, they replicate, avoiding detection by the host immune defenses. It is through these infected macrophages that the organisms then spread throughout the reticuloendothelial system and other organs [1,7]. The most effective immune response is mounted through adaptive immunity, mediated by the T lymphocytes and their interactions with the antigen presenting cells. Notably the most important cytokines involved are TNF-alpha and Interferon-gamma. This leads to activation of macrophages and leads to either, clearance of infection or formation of granulomas [8]. Although latent, the infection may be re-activated if adaptive immunity is impaired [8].

Risk factors for severe infection include HIV, hematological malignancies, transplant, corticosteroid therapy, extremes of age and congenital immuno deficiencies.

Signs and symptoms of disseminated histoplasmosis are nonspecific and include fever, malaise, anorexia, and weight loss. Patients may also present with hepatosplenomegaly, lymphadenopathy, pallor, petechiae, and skin ulcers. Labora-

tory studies typically reveal pancytopenia and elevated alkaline phosphatase levels, ESR, CRP, and lactate dehydrogenase. Severe disease may present with hypotension, Disseminated Intravascular Coagulation (DIC), renal failure, and respiratory distress [5,7]. Radiologic findings in the chest can often be normal but commonly present as a diffuse form of reticulonodular opacity. Other findings that may be seen are linear or irregular opacities. These may be accompanied by adenopathy, encountered frequently among immunocompetent individuals and less commonly among immunocompromised patients [9].

Severely immunocompromised patients often present acutely with fever, pancytopenia, severe respiratory distress, circulatory shock, coagulopathy and multiorgan failure involving the liver and kidneys [10]. The adrenal glands are one of the most frequently involved tissues in disseminated histoplasmosis and may be associated with adrenal insufficiency. Radiologic findings most commonly seen include bilateral adrenal gland enlargement associated with focal areas of hypoattenuation suggestive of necrosis or hemorrhage [11].

Among the various subtypes of disseminated histoplasmosis, chronic progressive Disseminated Histoplasmosis is one that affects the elderly with no known immunosuppression and has a more prolonged course [1]. It presents with pancytopenia, gastrointestinal tract lesions, hepatosplenomegaly, and elevated liver enzymes [5,7].

Our patient was initially evaluated for his cholestasis and lung lesion (initially thought to be due to an abscess). After the lung biopsy findings suggested histoplasmosis, a careful review of the patient's history was performed, which did not indicate any immunosuppression. He had no obvious risk factors (occupational or otherwise) concerning for histoplasmosis. Hence it was difficult to understand the cause for such a severe disseminated form of the disease. The only identifiable risk factors were his age and heavy alcohol use.

Gastrointestinal tract infection is known to occur but is normally asymptomatic or causes only vague abdominal pain and diarrhea. Although hepatic involvement is known to occur, a cholestatic pattern is extremely rare [12,13,14,15]. Abdominal CT findings in our patient included hepatomegaly and an indeterminate intrahepatic lesion. In a past study reporting the radiologic manifestations of disseminated histoplasmosis in a series of patients, the commonly seen abnormal but non-specific findings seen on an abdominal CT included hepatomegaly and splenomegaly. The liver enlargement was seen accompanying all the patients with splenic enlargement and a rare but specific finding suggestive of disseminated disease was diffuse splenic hypoattenuation; other radiologic findings that may be suggestive include lymph node enlargement and soft tissue density [16].

While transaminases may be raised, elevated alkaline phosphatase is one of the most prominent lab findings with values as high as $>$ 2100 U/L. A liver biopsy may be performed along with urine and serum histoplasma antigen studies to establish the diagnosis. Severity of cholestasis may function as a prognostic indicator in disseminated histoplasmosis [15]. Our patient underwent USG and MRCP to evaluate for obstruction but there was neither sign of obstructive disease nor any signs indicative of cirrhosis or alcoholic hepatitis. His bilirubin and ALP levels continued to rise and upon ruling out all other causes of obstructive liver disease, the CT- guided liver biopsy revealed severe histoplasmosis infiltration.

Histoplasmosis can be diagnosed via multiple different modalities. Biopsies of lesions using methenamine silver or periodic acid-Schiff stains can visualize *H. capsulatum* yeast [7]. Both urine and plasma antigens can detect infection, though they are less reliable when used in immunosuppressed patients. Antibody testing using immunodiffusion and complement fixation is commonly used as well but can be falsely negative in immunosuppressed patients or during acute infection [17]. Finally, blood cultures can grow *H. capsulatum* if hematogenous spread has occurred.

Disseminated histoplasmosis that is severe enough to require hospitalization should be initially treated with liposomal Amphotericin B [18]. When the patient is afebrile, and not requiring additional blood pressure or ventilator support, they may be transitioned over to itraconazole (normally after 1 to 2 weeks of Amphotericin B). The ideal duration of therapy with itraconazole has not been studied, but most sources recommend continuing treatment for at least a year. Itraconazole requires a highly acidic pH for absorption. For this reason, it should be taken with food and is often given with soda or cranberry juice. PPIs, H2 blockers, and other antacids should be avoided while taking itraconazole [19].

Conclusion

Disseminated histoplasmosis is a severe manifestation of Histoplasma capsulatum infection which should prompt a review of history and evaluation for underlying immunosuppression. It may vary greatly in presentation and therefore requires a high index of suspicion for timely diagnosis and treatment. This is a life-threatening condition that may require a multi-disciplinary approach to care.

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