

Disseminated Histoplasmosis Presenting as Fever and Jaundice

Dear Editor,

Outside of mid-western United States,¹ histoplasmosis is endemic in pockets of Asia (like Indonesia) and Europe (Italy, Hungary, Romania, Britain).² It is caused by *H. capsulatum*, a fungus found in barns, old houses or soil contaminated with bird droppings. Airborne spores infect those who inhale it. Disease manifestation is myriad, ranging from a sub-clinical infection to an organ-specific disease, such as acute pulmonary syndrome, cavitary lung disease to progressive disseminated histoplasmosis (PDH), the latter commonly seen in immunocompromised hosts, with human immunodeficiency syndrome.^{3,4}

We report an interesting case of cholestatic jaundice presenting to the physician as a diagnostic dilemma. Our subject was eventually diagnosed with progressive disseminated histoplasmosis after extensive evaluation. Uncommonly, histoplasmosis may present as cholestatic jaundice as in our case report. Also, PDH infrequently occurs in subjects with relatively normal immunity. Gastroenterologists practising in non-endemic regions will therefore need to be mindful of such unusual manifestations of the disease.

Case Report

A 59-year-old businessman from Jakarta, Indonesia, presented with fever of a month's duration associated with icterus and tea-coloured urine. He did not have any risk factors for jaundice, notably a history of seafood ingestion, sexual promiscuity, intravenous drug use, blood transfusions, anaemia, traditional medication or alcohol consumption. Neither was there any significant family history of note. Weeks prior to symptom onset, he had travelled to farmlands in Medan. He had undergone an abdominal computed tomography (CT) scan which revealed hepatomegaly and an endoscopic retrograde cholangiopancreatography (ERCP) was unremarkable.

He was referred to our institution for further investigations. Complete blood count revealed anaemia with normal leukocyte and platelet counts: haemoglobin 9.9 g/dL (12.9-16.7). Liver function test was abnormal: total bilirubin 260 µmol/L (5-30), conjugated bilirubin 194 µmol/L (0-5), alkaline phosphatase 528 U/L (40-130), albumin 26 g/L (38-48). Aspartate and alanine aminotransferase were normal. Prothrombin time and INR were prolonged: 20.8 seconds (12.0-14.8) and 1.69, respectively. C-reactive protein was elevated: 75 mg/L (0-10).

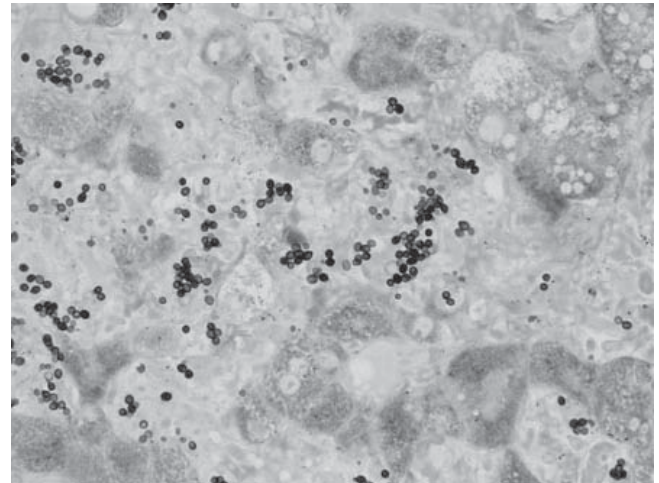


Fig. 1. Photomicrographs of liver-biopsy specimen. Gomori methenamine-silver stain (GMS). Cholestatic hepatitis with mixed portal inflammatory cellular infiltrates, including neutrophils. The Kupffer cells contain intracellular organisms with features of yeast forms averaging 2 to 3 µm in diameter. They stain positively with GMS. Occasional budding. There is no evidence of a mucin-positive capsule or any transverse septations. The features are suggestive of histoplasmosis.

Smears for acid-fast bacilli and malaria were negative, and the chest radiograph was unremarkable. Tests for viral and autoimmune hepatitis, primary biliary cirrhosis, Epstein-Barr virus, cytomegalovirus, leptospirosis and retrovirus were non-reactive. A set of blood cultures isolated *Enterococcus faecalis*. He was administered intravenous ampicillin and gentamicin. Further magnetic resonance cholangiopancreatogram (MRCP) confirmed a normal biliary tree. Echocardiography, colonoscopy and CT of the thorax were normal.

We performed a liver biopsy which was diagnostic for intracellular budding yeasts (Fig. 1), verified by similar findings on bone marrow aspirate. Given the epidemiological exposure, progressive disseminated histoplasmosis was suspected and he was started on amphotericin B. His fever promptly resolved with the initiation of treatment. Serum histoplasma antibody, urine antigen (8.45 EIA units, >1.0 positive) and fungal blood cultures later returned positive for *H. capsulatum* in subsequent weeks confirming the diagnosis.

Discussion

In the approach to jaundice, a predominantly elevated

conjugated bilirubin and alkaline phosphatase would favour a cholestatic cause. As such, ultrasound of the hepatobiliary system is useful. If the biliary ducts are dilated, ERCP is warranted for a confirmation of the diagnosis (e.g. choledocholithiasis), and therapy. However, if the ultrasound is normal, then subjects should be stratified based on the probability of a biliary obstruction. High probability subjects would benefit from a diagnostic ERCP; moderate probability subjects should undergo an endoscopic ultrasound/MRCP. Subjects who are of low probability or who have a normal biliary anatomy, are evaluated for causes of intrahepatic cholestasis.

These include infiltrative/systemic processes such as amyloidosis, malignancy and granulomatous diseases. Granulomatous diseases, include infections (e.g. mycobacteria, fungal), drugs (e.g. allopurinol) and systemic diseases (e.g. sarcoidosis, lymphoma). Other causes of cholestasis include paraneoplastic syndromes, atypical presentations of viral hepatitis and diseases of the bile ductules (e.g. primary biliary cirrhosis). Congenital cholestatic syndromes are unlikely in view of the elevated alkaline phosphatase. Should the diagnosis remain doubtful, a liver biopsy would be useful. This report illustrates an uncommon cause of cholestasis – histoplasmosis.

Clinching a diagnosis of histoplasmosis, especially one with atypical manifestations, can be challenging for the physician in a non-endemic region. Unfortunately, there is no pathognomonic disease manifestation. Non-invasive diagnostic assays, such as the urine histoplasma antigen and histoplasma antibody serology, are sensitive and rapid, but often unavailable in non-endemic regions. Fungal cultures are the gold standard, but positive results can be delayed by more than 4 weeks.² Given these limitations, the astute physician has to rely on a history of epidemiologic exposure and consider histopathology to make an early bedside diagnosis. Liver histology from our subject proved to be a rapid test, clinching the unexpected diagnosis of PDH.

Self-limiting histoplasmosis does not require treatment. However, therapy improves survival in PDH. Antifungal therapy is extremely efficacious, typically involving amphotericin B followed by itraconazole for 6 to 12 months' duration, with antigen levels monitored.⁵ Cholestasis will resolve spontaneously with treatment.

In conclusion, histoplasmosis should be considered in subjects from an endemic region presenting with cholestatic jaundice and fever. Liver histology is of diagnostic value when common causes of intrahepatic and extrahepatic cholestasis have been excluded.

REFERENCES

1. Springston JP. The birds. *Occup Health Saf* 1998;67:86-9.
2. Wheat LJ. Histoplasmosis: a review for clinicians from non-endemic areas. *Mycoses* 2006;49:274-82. Review.
3. Wheat LJ, Kauffman CA. Histoplasmosis. *Infect Dis Clin North Am* 2003;17:1-19, vii. Review.
4. Kurowski R, Ostapchuk M. Overview of histoplasmosis. *Am Fam Physician* 2002;66:2247-52. Review.
5. Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, et al. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. *Clin Infect Dis* 2000;30:688-95.

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