

# A case of *Histoplasma capsulatum* causing granulomatous liver disease and Addisonian crisis

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P Wong, S Houston, B Power, E Lalor, VG Bain. A case of *Histoplasma capsulatum* causing granulomatous liver disease and Addisonian crisis. *Can J Gastroenterol* 2001;15(10):687-691. A 56-year-old man with persistently elevated liver enzyme levels, fatigue, lethargy and a 9.0 kg weight loss over six months underwent a percutaneous liver biopsy that demonstrated multiple granulomas. Screening serologies were positive for histoplasmosis, and he was started on itraconazole treatment. He returned to hospital the same night with coffee-ground emesis and in Addisonian crisis requiring parenteral steroids and intensive care unit support. An abdominal computed tomography scan revealed bilaterally enlarged, nonenhancing adrenal glands suggestive of infarcts, presumed secondary to histoplasmosis. Treatment was initiated with amphotericin B, and *Histoplasma capsulatum* was cultured from his urine and cerebrospinal fluid. A serum immunodiffusion test was also positive for both H and M bands, indicating active infection with *Histoplasma* species. His serum and urine samples were also weakly positive for the antigen. Despite complications of renal failure, pneumonia and congestive heart failure, he recovered with medical therapy and was discharged home to complete a prolonged course of itraconazole therapy. While hepatic granulomas often reflect an occult disease process, the cause may remain undiscovered in 30% to 50% of patients despite exhaustive investigations. *H capsulatum* is an uncommon cause of granulomatous liver disease, and with its protean clinical presentation, a high index of suspicion is needed to make the diagnosis and avoid the potentially high fatality rate associated with disseminated infection.

**Key Words:** Addisonian crisis; Adrenocortical insufficiency; Granulomas; Granulomatous hepatitis; Histoplasmosis; Liver

## Cas d'*Histoplasma capsulatum* causant une granulomatosé hépatique et une crise addisonienne

**RÉSUMÉ :** Un homme de 56 ans présentant des taux d'enzymes hépatiques toujours élevés, de la fatigue, de la léthargie et ayant perdu 9 kg au cours des six mois précédents a subi une biopsie percutanée du foie, qui a révélé la présence de nombreux granulomes. Des tests sérologiques de dépistage ont donné des résultats positifs à l'égard de l'histoplasmosé, et le patient a commencé un traitement à l'itraconazole. Le soir même, il est retourné à l'hôpital, présentant des vomissements marc de café et une crise addisonienne, qui a nécessité l'administration de stéroïdes par voie parentérale et son admission aux soins intensifs. Une tomographie abdominale a montré deux glandes surrénales augmentées de volume, non stimulantes, évocatrices d'infarctus, probablement secondaires à l'histoplasmosé. Un traitement à l'amphotéricine B a donc été amorcé, et on a procédé à une culture d'*Histoplasma capsulatum* sur des prélèvements d'urine et de liquide céphalo-rachidien. Une épreuve d'immunodiffusion sérique s'est aussi révélée positive à l'égard des bandes H et M, signe d'infection active à des espèces d'*Histoplasma*. Le prélèvement d'urine et le sérum étaient également faiblement positifs à l'égard de l'antigène. Malgré des complications : insuffisance rénale, pneumonie et insuffisance cardiaque, le patient a récupéré et est retourné chez lui pour un traitement prolongé à l'itraconazole. Même si les granulomes hépatiques témoignent souvent d'un processus pathologique occulte, la cause reste inconnue chez 30 à 50 % des patients, et ce, malgré une exploration poussée. *H. capsulatum* est rarement cause de granulomatosé hépatique et, compte tenu de son tableau clinique variable, il faut une bonne dose de présomption pour poser le diagnostic et éviter la dissémination de l'infection associée à un taux potentiellement élevé de létalité.

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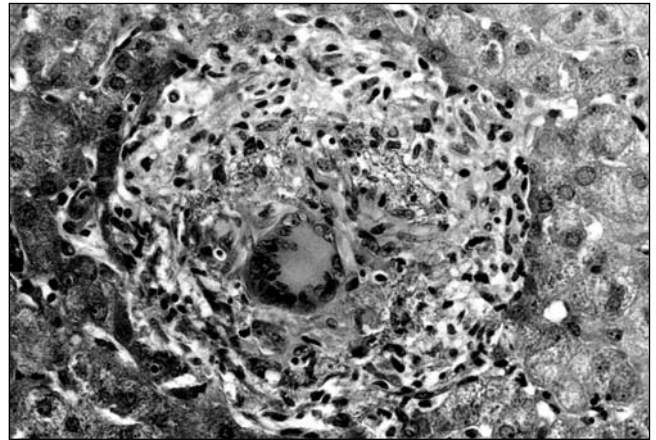
Hepatic granulomas have been reported in up to 15% of needle liver biopsy specimens and may indicate an underlying systemic process. The differential diagnosis for granulomatous liver disease is extensive and includes infections, sarcoidosis, drug and foreign body hypersensitivity reactions, autoimmune diseases and malignancy. 'Idiopathic' granulomatous liver disease still comprises a large percentage of cases in the modern era, despite improved diagnostic techniques.

### CASE PRESENTATION

A 56-year-old man with a history of lethargy, fatigue and abnormal liver enzyme levels was referred for evaluation of 'granulomatous hepatitis'. He had a 10-year history of disabling fatigue that had been diagnosed as 'chronic fatigue syndrome', and he had been unable to work as a university lecturer for approximately five years. Over the six months preceding the consultation, he experienced reduced mental clarity (with excessive fatigue, at times sleeping up to 20 h per day), anorexia and a 9 kg weight loss. Six years earlier, a ventriculoperitoneal shunt was placed for hydrocephalus of unknown etiology. It had been complicated by blockage on two occasions despite normal protein and glucose levels, and a normal cell count in the cerebrospinal fluid (CSF). No fungal culture was performed on these occasions. A recent computed tomography (CT) scan of his head was unchanged. There was no history of liver disease, but he had a remote history of nonintravenous drug use. He had no episodes of confusion or sleep reversal, or symptoms of fever or sweats. He had no recent travel history or prior known exposure to tuberculosis. He had no drug allergies, and his medications included testosterone and folic acid for his 'chronic fatigue', as well as some herbal supplements.

Over a six-month period, a progressive elevation of his liver enzyme levels was noted as follows: aspartate aminotransferase 58 to 66 U/L (normal levels less than 40 U/L), alanine aminotransferase 68 U/L (normal less than 50 U/L), alkaline phosphatase 118 to 435 U/L (normal 30 to 130 U/L) and gamma glutamyltransferase 121 U/L (normal less than 70 U/L). His bilirubin, albumin and coagulation profiles were normal. His erythrocyte sedimentation rate was 67 mm/h, and his ferritin concentration was 1053 µg/L. Viral screens for hepatitis A, B and C, as well as screens for human immunodeficiency virus, were negative. His thyroid-stimulating hormone, ceruloplasmin, alpha-1 antitrypsin, cortisol, testosterone and dehydroepiandrosterone levels were normal, as was his serum protein electrophoresis. A chest radiograph and ultrasound of the abdomen were unremarkable.

A percutaneous liver biopsy revealed numerous non-caseating granulomas with multinucleated giant cells (Figure 1). No foreign material was seen on polarized light, and stains for acid-fast bacilli and fungi were initially reported as negative. On the day of his visit to the liver clinic, screening serologies sent by his referring gastroenterologist returned positive for *H capsulatum*. His history at



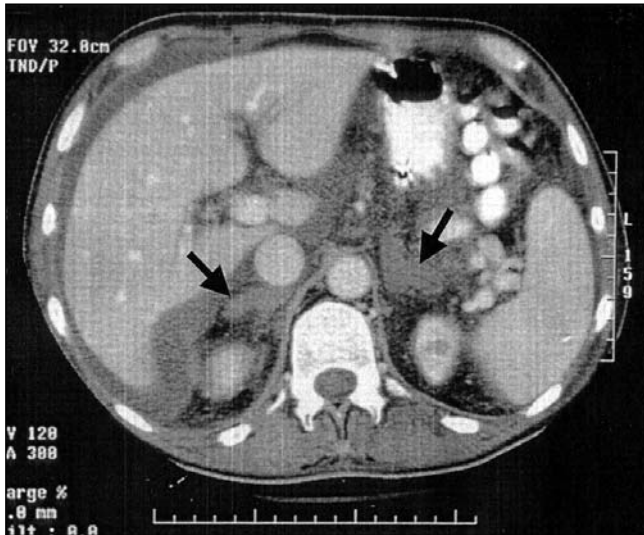
**Figure 1)** Percutaneous liver biopsy. Numerous noncaseating granulomas with multinucleated giant cells are seen. This slide demonstrates a typical noncaseating granuloma with a large, central, multinucleated giant cell. The surrounding liver tissue appears normal

that time revealed that he had lived in Indiana from 1964 to 1974.

The patient appeared to be underweight and had a resting tachycardia of 100 beats/min, with a blood pressure of 98/60 mmHg. His physical examination was otherwise unremarkable — his liver and spleen were not palpable, and he had no cutaneous stigmata of chronic liver disease. The Infectious Diseases service also reviewed him in consultation, and after obtaining a bone marrow biopsy and cultures, he was discharged home on oral itraconazole.

He returned later that evening to the emergency room disoriented and confused after experiencing coffee-ground emesis. Despite aggressive fluid challenge with 4 L of crystalloid, his blood pressure dropped from 100/68 mmHg to 80/40 mmHg, and he became tachycardic at 130 beats/min. His hemoglobin concentration was 131 g/L (normal range 140 to 180 g/L), and his white blood cell count was  $11.6 \times 10^9/L$  (normal range  $4.8$  to  $10.8 \times 10^9/L$ ). A fever of  $38.2^\circ C$  was noted. His physical examination was significant for inspiratory crackles on respiratory examination, and asterixis on neurological screening. His sodium concentration was 129 mmol/L and his potassium concentration was 6.4 mmol/L, consistent with Addisonian crisis. Despite hemodynamic support with dopamine and noradrenaline, his blood pressure remained low but responded after steroid administration. A chest x-ray demonstrated a right lower lobe pneumonia, but no features of old granulomatous disease. He was intubated and admitted to the intensive care unit, where he was started on amphotericin B for suspected disseminated histoplasmosis.

A gastroscopy revealed severe erosive esophagitis as the source of his coffee-ground emesis. A CT scan of his head was unchanged, showing multiple chronic lacunar infarcts but no hydrocephalus. An abdominal CT scan revealed bilateral pleural effusions with bibasilar consolidation, and a moderate amount of ascites. His adrenal glands were bilaterally enlarged and nonenhancing, consistent with infarcts or necrosis from adrenal histoplasmosis (Figure 2). A serum

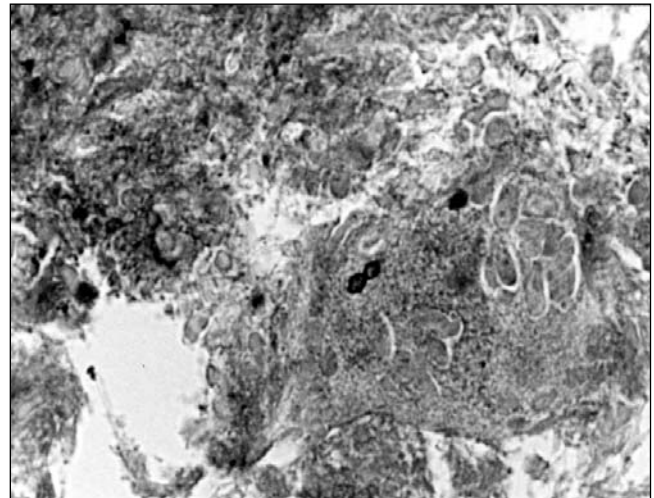


**Figure 2)** Abdominal computed tomography scan. A moderate amount of ascites is present. The adrenal glands (arrows) are markedly enlarged to about five times the normal size and are nonenhancing, and consistent with infarcts or caseous necrosis from adrenal histoplasmosis

immunodiffusion test was also positive for both H and M bands, indicating active infection with *Histoplasmosis* species. Esophageal, gastric and duodenal biopsies were negative for histoplasma on histology and culture. *Candida albicans* was cultured from a bronchoalveolar lavage. An examination of CSF from the patient's ventriculoperitoneal shunt showed a white blood cell count of 0 (normal less than  $5 \times 10^6/L$ ), a red blood cell count of  $1 \times 10^6/L$  (normal 0/L), a protein concentration of 0.25 g/L (normal 0.2 to 0.4 g/L) and a glucose concentration of 4.5 mmol/L (normal 2.2 to 3.9 mmol/L). Cultures of his CSF and urine produced *H capsulatum*, but his blood, liver and bone marrow cultures were negative. Histoplasma antigen was weakly positive in his urine and serum samples as well.

Antifungal therapy was switched to oral itraconazole as he improved. His hospital course was prolonged, requiring treatment for adrenal insufficiency, acute renal failure and pneumonia. Significant cardiac systolic dysfunction with an ejection fraction of less than 20% developed for unknown reasons, but this resolved during follow-up without residual deficits. After a month in hospital, he was discharged on replacement steroids and oral itraconazole.

The liver biopsy was obtained and rare fungal elements were identified after restaining with Grocott methenamine silver (Figure 3). He was doing well on last follow-up after completing a 12-month course of itraconazole, and had made a full recovery with normalization of all liver enzyme levels. Repeat magnetic resonance imaging of his brain showed no change in the previously noted white matter changes, and he has had no further problems with his shunt. The patient and his family report that his health status is better than it had been since the onset of his ill-defined fatigue more than a decade previously.



**Figure 3)** Liver biopsy restained with Grocott methenamine silver stain. Fungal elements are seen, demonstrating a budding yeast form typical of *Histoplasma* species. These were very sparse and seen only after additional sections were cut and examined

**TABLE 1**  
**Causes of hepatic granulomas infections**

Bacterial	Tuberculosis*, <i>Mycobacterium avium</i> -intracellulare, leprosy, brucellosis, tularemia, listeriosis, Bacillus Calmette-Guérin disease, salmonellosis, <i>Yersinia</i> species
Mycotic	Histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, toxoplasmosis, nocardiosis, candidiasis, actinomycosis
Parasitic	Schistosomiasis, toxocarasis, tonguworm, strongyloidiasis, ascariasis, leishmaniasis, visceral larva migrans, fascioliasis
Viral	Cytomegalovirus, Epstein-Barr virus, lymphogranuloma venereum, rickettsia, <i>Coxiella burnetii</i> (Q fever)
Spirochetal	Syphilis, Lyme disease
Drugs	Phenylbutazone, allopurinol, sulfonamides, sulfasalazine, penicillins, chlorpropamide, quinidine, methyldopa, hydralazine, cephalexin, phenytoin, procainamide, halothane, quinine, diltiazem, methimazole
Foreign substances	Beryllium, zirconium, silica
Malignancies	Hodgkin's disease, non-Hodgkin's lymphoma, renal cell carcinoma
Miscellaneous	Sarcoidosis*, primary biliary cirrhosis, Crohn's disease, Wegener's granulomatosis, polymyalgia rheumatica, jejunoileal bypass, hypogammaglobulinemia
Idiopathic*	

\*These are the most common diagnoses for granulomatous liver disease. Data from references 2 and 26



## DISCUSSION

Hepatic granulomas are a common finding, detected in 2.4% to 14.6% of all needle liver biopsies (1). They are a nonspecific entity with an extensive list of causes (Table 1), including infections, drugs, foreign material, autoimmune diseases and malignancy. Idiopathic granulomatous liver disease or 'idiopathic granulomatous hepatitis' are terms used when no cause is found on investigation (2). Tuberculosis and sarcoidosis account for 50% to 60% of cases of granulomatous hepatitis worldwide (2). Several authors have reported their institution's experience (3-11), and *H capsulatum* is an uncommon cause of granulomatous liver disease. McCluggage et al (1) in Ireland reported primary biliary cirrhosis and sarcoidosis as their most frequent etiologies, but no cases were due to histoplasmosis. Sartin et al (3) from the Mayo Clinic (Rochester, Minnesota) found idiopathic granulomatous disease as their most common diagnosis, followed by sarcoidosis, medications and tuberculosis. In the present study, histoplasmosis comprised 4.5% (four of 88) of cases. Smaller series in the literature have reported variable rates of histoplasma-associated granulomatous liver disease, likely reflecting regional endemic diseases, environmental exposures and local physician practices in the use of liver biopsy.

*H capsulatum* is usually acquired as a pulmonary infection after aerosolized spores are inhaled from soil contaminated by bird or bat droppings. In North America, endemic regions for the fungus include parts of southern Ontario and Quebec (12,13), and the Ohio and Mississippi River regions in the central United States. Population prevalence of histoplasmin skin test sensitivity reflecting past exposure often exceeds 50% in endemic areas (14). Outbreaks of histoplasmosis have been reported from Indianapolis, near the patient's former residence (15). However, histoplasmosis may present in nonendemic areas, presumably reflecting reactivation of previously acquired latent infection.

Primary infection with *H capsulatum* is most often asymptomatic or results in a nonspecific, self-limiting illness. Disseminated disease is thought to occur in about one of 2000 *H capsulatum* infections during outbreaks (15), although the rate may be much higher in immunocompromised individuals, particularly in those with advanced human immunodeficiency virus disease. Disseminated histoplasmosis has a protean presentation, reflecting its multisystem involvement. Malaise, weight loss, fevers, chills and sweats are common symptoms, with lymphadenopathy, hepatosplenomegaly and painless oral ulcers frequently seen on physical examination. Serious complications of anemia, leukopenia, thrombocytopenia, pneumonia, endocarditis (16), meningitis and cerebral mass lesions (17) are well described, and it remains unclear whether our patient's cardiac and neurological problems were related to the disseminated histoplasma infection. Gastrointestinal involvement beyond hepatosplenomegaly and oral ulceration is uncommon, but ileal and colonic ulceration mimicking inflammatory bowel disease (18,19), polypoid or mass lesions and bowel perforation have been reported. The adrenal glands are involved in over 80% (20,21) of patients

in autopsy series, but 5% to 10% of patients develop clinical adrenal insufficiency (22), secondary to ischemic injury of the gland from vascular thrombosis (23,24).

The sensitivity of culture varies with the site of disease involvement (16). Bone marrow and blood cultures are positive in up to 50% of patients (24). Sputum cultures are positive in only 10% to 15% of patients (25), but increase to 60% when cavitating lung disease is present, or higher if cultures are obtained by bronchoalveolar lavage. Cultured liver tissue is positive in less than 10% of granulomatous liver disease cases, but approaches 50% when fungal infections are the underlying cause. Hematoxylin and eosin or Wright-Giemsa staining can identify histoplasma in one-third of biopsies, but specialized stains such as Grocott methenamine silver can further improve detection. Unfortunately, because these stains lack specificity for *H capsulatum*, other fungal species may be mistakenly identified for the organism.

Serology is a valuable diagnostic tool but may be falsely negative in immunocompromised patients with disseminated histoplasmosis. Failure to develop a diagnostic titre of complement fixation antibody occurs in 30% to 50% of these patients. In immunocompetent patients with primarily lung involvement, antibodies are detectable as early as three weeks after infection in 5% to 15% of individuals, and in 75% to 95% by six weeks, especially if the patients become symptomatic. Titres less than 1:16 may require additional testing to confirm histoplasma, but antibody levels greater than 1:32 are highly suggestive of active infection (23). Unfortunately, antibody titres may remain elevated for years and are less useful in monitoring the disease. Immunodiffusion studies (immunoprecipitating assays) may improve sensitivity by detecting antibodies to M or H antigens from cultures. Although antibodies to M antigen are detectable in 50% to 80% of patients two to four weeks after the development of complement fixation antibodies, the antibody may persist for years after resolution of the infection. Antibodies to the H antigen are more specific and signify active infection when present, but have a less than 10% sensitivity (16). DNA probe technology is promising and rapidly evolving, with its main advantage being the ability to identify a culture isolate within hours to guide appropriate therapy (16). If serological screening is negative but clinical suspicion remains high, biopsy of the most accessible, appropriate tissue is warranted.

Treatment of granulomatous liver disease depends on the cause, ranging from antifungal therapy in our patient with histoplasmosis to chemotherapy for those with an underlying malignancy. Untreated disseminated histoplasmosis has a mortality rate of 100%, with disseminated intravascular coagulopathy, hemorrhage and bacterial infections being the usual cause of demise, likely from the pancytopenia commonly seen (16). Amphotericin B is usually reserved for patients with more acute illness or serious organ involvement, whereas azole therapy (itraconazole, ketoconazole and fluconazole) is often used in clinically stable patients as outpatient therapy. The natural history and

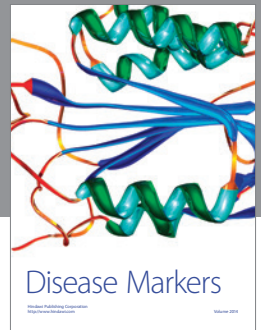
management of 'idiopathic' patients remain unclear, especially when an unknown percentage of patients can have spontaneous improvement.

Determining the underlying cause of hepatic granulomas can be difficult, and 30% to 50% of cases remain undiagnosed. Although it is reasonable to target investigations to the most common causes (ie, infection and sarcoidosis),

empirical drug trials with antituberculous drugs or corticosteroids should be avoided as much as possible to prevent compromising a complete evaluation. *H capsulatum* is an uncommon cause of granulomatous liver disease with a protean clinical presentation. A high index of suspicion is needed to make the diagnosis and avoid the potentially high fatality rate associated with disseminated infection.

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