Case Report

Acalculous Cholecystitis caused by *Histoplasma capsulatum* in a severely immunosuppressed HIV-infected patient

Jorge Alave[1], Beatriz Bustamante[1,3], Leslie Soto[2,3], Jaime Cáceres[4], Carlos Seas[1,3]

[1]*Departamento de Enfermedades Infecciosas, Tropicales y Dermatológicas, Hospital Nacional Cayetano Heredia, Lima, Peru*
[2]*Departamento de Medicina Interna, Hospital Nacional Cayetano Heredia, Lima, Peru*
[3]*Instituto de Medicina Tropical Alexander von Humboldt. Universidad Peruana Cayetano Heredia, Lima, Peru*
[4]*Departamento de Patología, Hospital Nacional Cayetano Heredia, Lima, Peru*

Abstract
Billiary tract involvement in the course of disseminated histoplasmosis has been rarely reported. Here we present a severely immunosuppressed HIV-infected patient who presented with symptomatic acalculous cholecystitis caused by *Histoplasma capsulatum*.

Key words: histoplasmosis; HIV; billiary tract

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Introduction

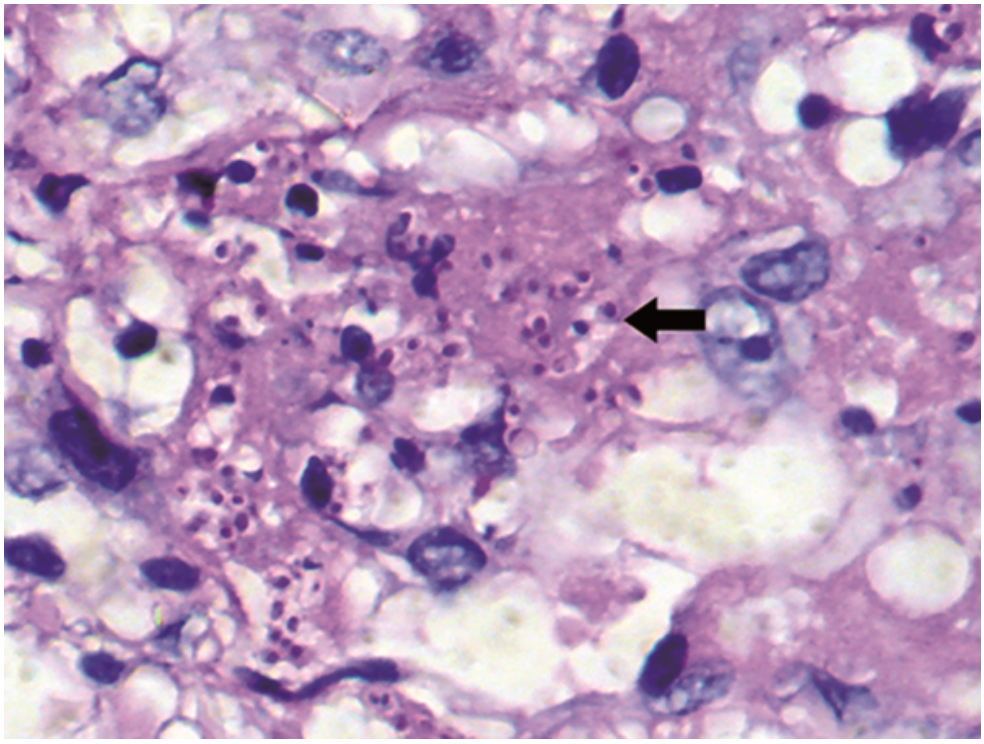
Biliary tract involvement is a well-recognized complication of advanced HIV infection [1,2]. HIV-associated cholangiopathy and acalculous cholecystitis are the most common clinical manifestations of biliary affection in these patients, and cytomegalovirus and *Cryptosporidium sp.* are the most common causative agents [3]. Infections with *Histoplasma capsulatum* are also well-known complications of advanced HIV infection, presenting with widespread involvement and overwhelming severity [4]. Biliary tract involvement by *H. capsulatum* has been rarely reported in both HIV and non-HIV infected patients [5]. We report a case of acalculous cholecystitis in the course of disseminated histoplasmosis in a severely immunosuppressed HIV-infected patient.

Case report

A 23-year-old HIV-infected male patient was transferred-to our hospital for evaluation of persistent fever, despite receiving standard treatment for suspected smear negative pulmonary tuberculosis for one month. The patient presented to the referring hospital with a three-week history of fever, cough and weight loss. Laboratory evaluations at that time included several negative sputum smears for acid-fast bacilli and fungi, and positive ELISA and Western blot tests for HIV infection. The CD4 cell count was 33 cells/μl, and the viral load 268,000 copies/ml.

The patient was born in the rainforest of Peru, but was living in Lima for the last eight years, and denied history of recent travel. The physical examination on admission to our hospital revealed a febrile patient in no acute distress; several macular violaceous lesions were noticed on the face, chest and upper extremities. No lymphadenopathy or visceromegaly was detected. Diffuse and bilateral pulmonary rales were heard on auscultation. Laboratory examinations revealed mild normocytic-normochromic anemia (hemoglobin of 10g/dl); leukopenia (total WBC of 3140 cells/mm3 with 86% neutrophils and 10% lymphocytes); mild thrombocytopenia (168,000 cells/mm^3); very high LDH serum values (20,000 IU/dl); and mildly elevated liver enzymes (ALT was 1.5 times above normal limit). The chest X ray revealed a diffuse interstitial infiltrate involving predominantly the lower lung fields. Repeated Ziehl-Neelsen stains of sputum samples were negative. Giemsa stains of a sputum sample and of a bone marrow aspiration were positive for intracellular yeasts compatible with *H. capsulatum*. A serologic immunodiffusion test was

Figure 1. Histopathological section of the gallbladder stained with PAS.



Gallbladder section showing inflammatory reaction in the subserosal layer and multiple small intracellular yeast forms of approximately 2μm (PAS stain, 1000x).

positive for band M of *H. capsulatum*, and bone marrow culture yielded *H. capsulatum*. The patient was started on intravenous amphotericin B deoxycholate at the dose of 1mg/kg/d. Two days after initiating treatment the patient complained of severe right upper quadrant pain, nausea and vomiting. Marked abdominal guarding and positive Murphy sign were found on physical examination. An abdominal ultrasound revealed thickening of the gallbladder wall surrounded by edema, but no gallstones or dilatation of bile ducts were observed. A laparoscopic cholecystectomy was performed. Histopathological evaluation of the gallbladder showed an inflammatory reaction mainly composed by histiocytes with intracellular yeasts consistent with *H. capsulatum* (Figure 1). The patient received two weeks of amphotericin B deoxycholate (total cumulative dose of 720 mg) followed by oral itraconazole. Combination antiretroviral therapy with stavudine, lamivudine, and ritonavir boosted atazanavir was started four weeks after. The clinical evolution was favorable; the last evaluation of the patient when he was receiving six months of treatment disclosed a CD4 cell count of 59 cells/μl and a viral load of 198 copies/ml.

Discussion

Histoplasmosis is a deep mycosis with worldwide distribution. Clinical manifestations of histoplasmosis are diverse, ranging from acute self-limited pulmonary involvement occurring in travelers exposed to aerosol acquired infection, to disseminated disease, which results from reactivation of latent foci and is mainly observed in immunodeficient hosts [6,7]. Progressive disseminated histoplasmosis (PDH) is a severe presentation of histoplasmosis occurring predominantly in immunosuppressed patients [8]. The estimated lifetime incidence rates of PDH in HIV-infected patients living in endemic areas is 5-20% [9]; 95% of these infections occur in patients with CD4 cell counts below 150 cells/μl [10]. PDH may follow an acute and usually fulminant clinical course or a more protracted and indolent course over several months [6]. The reticuloendothelial system is preferentially affected and manifested with generalized lymphadenopathy and visceromegaly, but widespread involvement of the kidneys, heart, skin and the CNS has been documented [4]. Gastrointestinal involvement has been recognized in 70-90% in necropsy studies of patients with PDH [11]. Affection of the terminal ileum and of the

lymphatic tissue surrounding the small intestine was the hallmark of gastrointestinal histoplasmosis in these reports. Interestingly, clinical evident manifestations of disease were rare in these patients, being reported in only 3-12% [5]. Reasons for the dissociation between clinical manifestations and pathological involvement are likely due to very subtle and non-specific clinical manifestations or underdiagnosis.

Biliary tract involvement in the course of histoplasmosis and PDH has been rarely reported. Two previous reports documented extra-hepatic biliary tract obstruction in two non HIV-infected pediatric patients who presented with abdominal pain as the main clinical manifestation [12,13]. One of these cases was a six-year-old boy with lymphoblastic leukemia [12], and the other one was a ten-year-old girl with no recognized immunosuppressive conditions [13]. The largest case series published to date of biliary tract involvement in HIV-infected patients did not document any case of PDH among 107 AIDS patients who underwent cholecystectomy [14]. Two subsequent reports documented biliary tract involvement in the course of PDH in HIV-infected patients [15,16]. In one of these reports, a 20-year-old female severely immunosuppressed patient, with a past history of PDH, non-compliant to anti-retroviral therapy (last CD4 cell count was 3 cells/μl) presented for evaluation of epigastric pain, nausea, vomiting and fever of five days duration. A duodenal ulcer with associated dilatation of the common bile duct presumably due to extrinsic compression of either adjacent lymph nodes or from a fluid collection within the neighboring intestinal wall was documented [15]. The second report described thickening of the duodenum with an erythematous and friable duodenal mucosa, dilatation of intra and extra-hepatic bile ducts, and distal stenosis of the common bile duct, which were observed in a 34-year-old male patient who presented with abdominal pain and weight loss two months after starting antiretroviral therapy [16]. A CD4 count of 12 cells/μl and a viral load < 48 copies/ml were documented on admission. The clinical presentation after initiation of antiretroviral treatment suggested immune reconstitution inflammatory syndrome of unmasking histoplasmosis in this case. Our patient clinically differed from these two previously reported HIV-infected cases. He developed the sub-acute and progressive form of PDH with evidence of pulmonary and bone marrow involvement, and presented suddenly with acute symptomatic acalculous cholecystitis with no evidence of bile duct involvement. Abdominal ultrasound was a helpful diagnostic tool in our patient and a laparoscopic cholecystectomy was indicated for his treatment. Further histopathological studies confirmed the gallbladder invasion by *H. capsulatum*. Intestinal involvement in this case could not be ruled out as intestinal endoscopies were not performed.

To our knowledge, this is the first report of PDH presenting with symptomatic acalculous cholecystitis in HIV-infected patients. Gallbladder involvement should be incorporated in the list of gastrointestinal organs affected in the course of PDH.

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Corresponding author
Carlos Seas, MD
Universidad Peruana Cayetano Heredia
Av. Honorio Delgado 430, Lima 31, Peru
Telephone: 51-1-4823910
Fax: 51-1-4823404
Email: cseas2@gmail.com

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