Biliary Diseases in HIV

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Manifestations of human immunodeficiency virus infection range from acute primary infections to life threatening symptomatic diseases that result from opportunistic infections. A Medline search was performed using the terms AIDS cholangiopathy, HIV hepatobiliary disease, HIV/AIDS acute acalculous cholecystitis, and AIDS sclerosing cholangitis to review the latest articles on biliary disease in HIV. These diseases fall into three categories: [1] AIDS cholangiopathy, [2] Acalculous cholecystitis, and [3] non-HIV related disease of the biliary system. This review paper will concentrate on the etiology, clinical presentations, diagnoses and treatment options of AIDS cholangiopathy and acalculous cholecystitis. Prior to the AIDS epidemic, diseases of the biliary tree with opportunistic organisms, such as Cryptosporidium and cytomegalovirus, were mostly unknown. While endoscopic retrograde cholangiopancreatography provides symptomatic relief in AIDS cholangiopathy, the availability of highly active antiretroviral therapy since 1996 is the main protective factor.
ETIOLOGY
The exact prevalence of AC is unknown. A recent Indian study showed an incidence of 0.9% amongst 2,806 patients with HIV from 2003 to mid-2009, with the median age of diagnosis being 43 years. In comparison, the average age of AC diagnosis was 37.4 (range 21–58 years old) in the United States for the same period. It is likely that AC is an infectious form of sclerosing cholangitis. Cryptosporidium parvum is the most common organism associated with AC. Other pathogens found in AC include cytomegalovirus (CMV), Giardia lamblia, Mycobacterium avium-intracellulare, Cyclospora cayetanensis, Isospora belli, Histoplasma capsulatum, and microsporidium. Specifically, microsporidia accounts for only 10% of AC cases with Enterocytozoon bieneusi being much more common than Encephalitozoon intestinalis.

PATHOPHYSIOLOGY
Under normal conditions the human biliary tree is sterile despite its communication with the enteric flora of the small intestine. A recent article of an in-vitro model of human biliary tract cryptosporidiosis demonstrated that recombinant HIV-1 Tat protein diminishes cholangiocyte expression of Toll-like receptor (TLR) 4, an important pathogen-recognition receptor. By this process patients with AIDS may be more susceptible to Cryptosporidium parvum, as well as other opportunistic infections.

DIAGNOSIS
Clinical
Regardless of the opportunistic organism involved, the clinical manifestations of AC present similarly. Specifically, AC presents with right upper quadrant (RUQ) and/or midepigastric abdominal pain in 90% of patients. Other symptoms include fever, nausea, vomiting and diarrhea. Diarrhea occurs because of small bowel involvement. In one study of AIDS patients with diarrhea due to Cryptosporidium, 23% developed biliary tract disease. In addition, three-quarters of AC patients experience significant weight loss and jaundice is present in 10% of patients with associated pruritus.

Laboratory Studies
Patients with AC typically present with CD4 count <100/mm3. A cholestatic pattern of liver enzyme abnormality is seen in the majority of patients, characterized by elevation of gamma-glutamyl transferase in 90% and an increased alkaline phosphatase of 700–800IU/L. Most AC patients also have mild increases in transaminases and total bilirubin, often less than twice the upper limit of normal. However, nearly 20% of patients with documented biliary tract abnormalities on cholangiography have normal liver function tests.

Abdominal Ultrasound
Ultrasound, the most cost-effective initial study, demonstrates abnormalities in 75% of patients with AC. Its sensitivity ranges from 75–97% and specificity goes up to 100%. The most common findings on an abdominal ultrasound include common bile duct dilatation in 65–75% of cases, and thickening of the common bile duct wall in 20–40%. In addition, an echogenic nodule at the distal end of the common bile duct is commonly seen on ultrasound, which correlates with edema of the papilla of Vater on ERCP. Following a positive or a negative ultrasound with symptoms suggestive of papillary stenosis, a more accurate test such as MRCP or ERCP is recommended.

ERCP
ERCP is the most definitive test to diagnose AC, as well as a therapeutic means to provide symptomatic relief to patients with papillary stenosis. On ERCP four common patterns of cholangiographic abnormalities are seen: papillary stenosis and intra/extrahepatic sclerosing cholangitis alone is seen in 36% and ≤15% of the patients respectively, papillary stenosis combined with sclerosing cholangitis in 44%, and isolated long extrahepatic duct stenosis or stricture in 5%. Papillary stenosis is defined as the presence of a 2–3 mm long distal common bile duct stricture, a threefold
elevation of serum alkaline phosphatase, proximal extrahepatic biliary dilation to more than 10 mm, and a delayed contrast drainage for approximately 30 minutes.\textsuperscript{19}

Identifying the opportunistic infection will help dictate the appropriate medical treatment. Endoscopic mucosal biopsies of the small bowel and papilla, ampullary biopsies after sphincterotomy, brush cytology of the bile duct, bile sampling, and stool studies are important diagnostic features for identifying the opportunistic infection\textsuperscript{13,23} In a study of 15 patients, successful identification was highest after obtaining multiple duodenal and papillary biopsies and bile sampling, with \textit{Cryptosporidium} identified in 57\% of cases, \textit{CMV} in 28\% and microsporidia in 7\%.\textsuperscript{13}

Severity of the abdominal pain can help differentiate the location of the lesion. Specifically, papillary stenosis usually presents with the most severe abdominal pain, while intra/extrahepatic sclerosing cholangitis without papillary stenosis is associated with milder abdominal pain.\textsuperscript{15}

The intrahepatic duct abnormalities of AC parallel those of sclerosing cholangitis; both yield focal biliary stenosis with moderate segmental dilatations that produce a beaded appearance associated with diminished arborization or pruning of the peripheral branches.\textsuperscript{31,33} While the diverticular outpouchings, sacculations, and high-grade proximal strictures of the extrahepatic ducts are typical of primary sclerosing cholangitis, they are mostly absent in AC.\textsuperscript{34} A moderate ductal dilatation, which is associated with irregular margins and nodules, is more typical of extrahepatic ductal manifestations of AC.\textsuperscript{34}

\textbf{MRI}

\textit{ERCP} as a diagnostic test is unpopular currently and magnetic resonance cholangiopancreatography (MRCP) has been recommended to study AC, although there are no established diagnostic criteria. MRCP demonstrates dilatation of the common bile duct with distal tapering that is associated with papillary stenosis.\textsuperscript{35}

\textbf{CT Scan of Abdomen}

Intrahepatic and/or extrahepatic bile duct dilatation can be seen on CT or ultrasound in 81\% of patients.\textsuperscript{15,19} CT scanning may demonstrate intrahepatic ductal dilation better than ultrasound, but it is less sensitive in detecting common bile duct wall thickness and strictures.\textsuperscript{25,33}

\textbf{MANAGEMENT}

Although sphincterotomy via ERCP provides symptomatic relief in 87–100\% of AC patients,\textsuperscript{13,27,28} it does not improve the length of survival.\textsuperscript{4} Even after sphincterotomy, serum alkaline phosphatase (ALP) may continue to rise, indicating a continuing progression of intrahepatic disease.\textsuperscript{15,28} Biliary stents and balloon dilation of strictures are potentially successful methods of treatment in some patients. However, such modalities are limited to case reports only and, therefore, require large randomized controlled trials to estimate their efficiency. For example, Cordero et al. reported on a 35-year-old man with cryptosporidial AC whose pain did not improve with endoscopic biliary sphincterotomy, antimicrobial therapy, and HAART, but did resolve four days after a plastic biliary stent was placed.\textsuperscript{36} Similarly, an AC patient with microsporidia reported by Sheikh et al. described in detail below, improvements on labs and severe stricturing of the extrahepatic and intrahepatic ducts were seen only after balloon dilation followed by a biliary stent placement.\textsuperscript{24}

Medical consensus holds that treatment of most opportunistic infections in AC does not improve symptoms or change cholangiographic abnormalities; however, in few isolated instances positive outcomes have been reported.\textsuperscript{27–29} For example, Hamour et al. reported an AIDS patient with intrahepatic sclerosing cholangitis who had cryptosporidial oocysts demonstrated in bile; intravenous therapy with paromomycin followed by oral letrozuril resulted in clinical improvement.\textsuperscript{37} Similarly, Sheikh et al. described a case of an AIDS patient with \textit{E. intestinalis} sclerosing cholangitis who had successful eradication of the organism with albendazole and clinical improvement.\textsuperscript{38} However, on repeat cholangiography progressive bile duct injury with stricturing was revealed requiring biliary sphincterotomy and stent placement.\textsuperscript{24} Treatment for \textit{CMV} with gancyclovir and foscarnet is nevertheless ineffective in patients with AIDS cholangiopathy.\textsuperscript{13,27}
Ursodeoxycholic acid has also been used as an additional treatment of AC. Studied in a small number of patients with AC where no ERCP follow-up was performed, ursodeoxycholic acid produced an improvement in symptoms and a fall in serum ALP, as well as gamma-glutamyl transferase.39

Combination antiretroviral therapy can profoundly suppress viral replication and subsequently lead to elevation in CD4 count.40,41 In a study by Ko et al., 13 of the 94 patients were on HAART therapy. Of the 13 patients, three died and amongst the remaining 10 patients some survived for more than 5 years. These findings suggest that the outcome of AC depends on the status of the underlying AIDS.4 In the most recent study the median survival was 34 months and is attributable to treatment with HAART following AC diagnosis.16 Development of AC while on HAART therapy may be a sign of worsening disease from either immunosuppression or antiviral resistance.

PROGNOSIS

Mortality is mostly determined by the natural history of AIDS and it is unlikely that AC plays any part therein. Ko et al., in a study of 94 patients with ERCP proven AC from 1983 to 2001, researched on the prognostic factors. The study looked at gender, age, race, the year of AIDS diagnosis and cholangiopathy, CD4 count at the time of the ERCP, liver enzyme abnormalities, status of antiretroviral treatment, along with the history of opportunistic infections.4 The results showed that ERCP findings and the performance of sphincterotomy did not influence the prognosis.4 In terms of laboratory data, normal or slightly elevated serum alkaline phosphatase was associated with a better outcome, whereas high levels (specifically >1000 IU/L) were associated with increased mortality.4 The utility of CD4 lymphocyte count to establish prognosis is controversial.4,12,14 Concomitant opportunistic infection in AC, whether focal or systemic, is a poor prognostic factor, especially if the infection is with cryptosporidiosis.4 In the Devarbhavi et al. study, the median survival time from the point of AC diagnosis was 34 months, which is better than the 4 to 9 month range reported in previous studies, and is likely to be due to HAART therapy.12,13,16,28 HIV viral load has not been studied as a marker for prognosis of AC.

Acalculous Cholecystitis

ACC is defined as an acute necroinflammatory disease of the gallbladder in the absence of cholelithiasis, which has a multifactorial etiology.42,43 The actual incidence of acalculous cholecystitis in HIV patients is unknown. ACC normally develops in the intensive care unit setting in patients with multisystem failure, sepsis, people on TPN, burn and trauma victims.43–45 Patients with AIDS and acalculous cholecystitis typically have end-stage HIV disease with low CD4 counts, coexisting opportunistic infections, and significant malnutrition. In addition, the gallbladder in patients with AIDS is predisposed to inflammation and infection with fungi, bacteria and viruses and, therefore, ACC may develop in these patients as well.46

Etiology

The first case of ACC was reported in 1984 by Blumberg et al. in a 29-year-old heterosexual man with AIDS and acute acalculous gangrenous cholecystitis associated with cytomegalovirus and Cryptosporidium.46 The likely organisms implicated are cytomegalovirus, Cryptosporidium, microsporidia, Salmonella enteritidis, Pneumocystis carinii, Campylobacter, Isospora belli, and Candida albicans.47-50 However, in as much as 53% of patients no etiologic agent is identified after extensive microbiologic evaluation.8,23,31,52 ACC can also be caused by obstruction of the cystic duct, due to Kaposi’s sarcoma.9

The first major report on ACC was made by French et al. and involved 136 patients with gallbladder disease who underwent cholecystectomy over a 6-year period at a tertiary referral center.52 Of the 136 patients, 107 had AIDS and 29 were HIV-seropositive patients without AIDS.52 Prior to this study there were only isolated case reports.7,8,46 French et al. reported that opportunistic infections were more common in patients with ACC in comparison to AIDS patients with cholecystitis associated with cholelithiasis. Most patients with biliary cryptosporidiosis also had intestinal involvement, but patients with a CMV infection in the gallbladder did not
show an infection elsewhere. Twelve of the 72 patients with ACC had disseminated Myco-bacterium avium complex infection and 10 out of 12 had no opportunistic infections of the gallbladder.

**DIAGNOSIS**

**Clinical**

The diagnosis of ACC is clinical and should be high on the differential when HIV patients complain of RUQ pain and present with RUQ tenderness, unexplained fever or signs of peritonitis on physical examination. French et al. documented right upper quadrant pain in 90%, nausea in 83%, diarrhea in 59% and weight loss in 41% of patients.

**Laboratory studies.** Serum bilirubin is usually normal, serum alkaline phosphatase is elevated (mean 293 IU/L) and ALT and AST are either normal, or mildly elevated. However, French et al., noted that when the gallbladder exhibited CMV and cryptosporidia infection together, the serum alkaline phosphatase levels (mean 479 IU/l) were higher than when the gallbladder was free of opportunistic infections.

**Imaging studies.** Radiologic diagnostic criteria have been developed for the use of computerized tomography, ultrasound and hepatobiliary iminodiacetic acid scan. The US and cholescintigraphy are the most commonly used imaging modalities to diagnose ACC.

**Ultrasound.** Ultrasound is usually the modality of first choice due to its easy repeatability, availability, cost, and portability to the bedside. Signs of ACC on ultrasound usually include pericholecystic fluid, intraluminal gas, gallbladder wall thickening ≥3.5 mm, sloughed mucosal membrane, echogenic bile, subserosal edema without the presence of gallstones, and hydrops. In general, the most studied and cited criteria for ACC is the triad of gallbladder wall thickening, echogenic bile and hydrops. The triad has a sensitivity of 50% and a specificity of 94% in the general population. Patients with AIDS often have asymptomatic thickening of the gallbladder wall. The cause is unknown and may represent intrinsic dysfunction or opportunistic infection that can induce ACC.

**HIDA**

HIDA scan radiolabeled with technetium 99m may show a non-functioning gallbladder. HIDA has a well-established diagnostic criteria for ACC with radionuclide cholescintigraphy, morphine cholescintigraphy, and cholecystokinin augmented HIDA as the three modalities used for the diagnosis of acute ACC. If the gallbladder is not visualized one hour after the radiolabeled technetium is injected, the study is considered positive. However, radionuclide cholescintigraphy HIDA is prone to false positive rates which has led some to recommend morphine cholescintigraphy confirmation. When a morphine injection is used, a positive study results if the gallbladder is not visualized after 30 minutes. HIDA scan showing a ‘nonvisualization’ of the gallbladder within the abovementioned timespan suggests the presence of ACC. Furthermore, cholecystokinin augmented HIDA can be used to exclude ACC. To explain, the normal response of the gallbladder to cholecystokinin injection is to contract and empty, but the gallbladder in ACC is unlikely to respond. French et al., reported that the diagnosis of ACC was based on decreased gallbladder contractility in response to cholecystokinin injection in 18 of their patients, all of whom had both a normal abdominal ultrasound and HIDA scan.

**CT**

The diagnostic criteria of CT is similar to that of an ultrasound and it may also demonstrate other intra-abdominal processes that would not be seen by an ultrasound.

**MRI**

MRI is not widely used for the diagnosis of ACC. On a contrast enhanced T1-weighted fat-saturated image, ACC is best shown with increased enhancement and thickening of the gallbladder wall.

**Management**

The treatment of choice is cholecystectomy. Surgery should not be withheld because of advanced AIDS.
cutaneous CT or ultrasound guided cholecystostomy can be performed for gallbladder decompression in ACC patients who are extremely ill or pose a high surgical risk since it is less invasive, does not require general anesthesia, and can serve as definitive therapy or a temporizing procedure until the patient is stable enough to undergo cholecystectomy. If cholecystectomy is performed the resected specimen should be sent for microbiologic and histopathologic evaluation.

Prognosis
Complications from ACC include perforation, peritonitis and necrosis. Mortality in this disorder can be significant if the diagnosis is delayed and gangrene and perforation develop as a result. Post-operative mortality for all cholecystectomies in HIV seropositive patients ranges from 2–22%. Most of the deaths in the higher range were the result of complications from prolonged hospital stays. The CD4 lymphocyte count did not influence mortality but was associated with a longer length of stay.

Conclusion
1. Since the advent of antiretroviral therapies, the mortality rate of HIV seropositive patients has dramatically decreased.
2. The two main HIV-related biliary diseases are AIDS cholangiopathy and acalculous cholecystitis.
3. The four types of cholangiographic abnormalities seen in AC are papillary stenosis, intra/extrahepatic sclerosing cholangitis, combination of papillary stenosis and sclerosing cholangitis, as well as extrahepatic duct strictures.
4. Ultrasound is the most cost-effective initial study to diagnose AC.
5. ERCP is helpful for diagnosis and reduction of pain in patients with AC, however, it does not extend survival.
6. Since the disorder is becoming a rarity, ERCP may be indicated in patients who are symptomatic and with papillary stenosis on MRCP.
7. In order to treat AC, emphasis should be placed on raising the CD4 count and lowering the viral loads.
8. Affected patients with ACC usually present with right upper quadrant pain in a setting of cholestatic pattern of lab abnormalities.
9. The most common laboratory abnormalities seen in ACC are significant elevation in ALP with usually normal or only mildly elevated transaminases.
10. The main treatment option for ACC is cholecystectomy.

References
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