Papillary Stenosis and Sclerosing Cholangitis in the Acquired Immunodeficiency Syndrome

DAVID J. SCHNEIDERMAN, M.D.; JOHN P. CELLO, M.D.; and FAYE C. LAING, M.D.; San Francisco, California

Eight homosexual men with the acquired immunodeficiency syndrome (AIDS) presented with clinical, biochemical, and radiologic features of stenosis of the papilla of Vater and sclerosing cholangitis. This newly recognized complication of AIDS produces abdominal pain, nausea, and vomiting and may predispose patients to superimposed bacterial cholangitis. Marked elevation of serum alkaline phosphatase levels and lesser changes in hepatic aminotransferase levels are common. Although abdominal ultrasonography and computed tomography detect ductal abnormalities, endoscopic retrograde cholangiography best shows precise ductal irregularities and provides therapeutic intervention. Prompt relief of symptoms follows endoscopic sphincterotomy, often with resolution of biochemical evidence of cholestasis. Biliary tract infection with cytomegalovirus or cryptosporidia and resultant viral or coccidial cholangitis are the proposed pathophysiologic mechanisms.

BILIARY TRACT DISEASE has been reported infrequently as a complication of the acquired immunodeficiency syndrome (AIDS). Acalculous cholecystitis has been described in association with cytomegaloviral and cryptosporidial infection (1, 2), and disorders of the intrahepatic and extrahepatic bile ducts similarly have been noted rarely in patients with AIDS. Pitlik and coworkers (3), in a review of human cryptosporidial infection, described the cases of two patients with AIDS with cholestasis, dilated bile ducts, and stenosis of the papilla of Vater documented by percutaneous cholangiography.

In recent years, we have seen eight patients with AIDS with papillary stenosis and obstruction of the common bile duct. Moreover, all patients had concomitant irregularities in the proximal intrahepatic ducts with focal stricturing, beading, and "pruning" of the terminal ductular branches as is seen in sclerosing cholangitis. These concurrent intrahepatic and extrahepatic ductular abnormalities have only recently been described in three patients with AIDS (4), but prolonged symptomatic relief after endoscopic sphincterotomy has not been documented to date.

Patients and Methods

Between October 1983 and January 1986, eight patients with AIDS and features of papillary stenosis and sclerosing cholangitis were evaluated at the San Francisco General Hospital. All patients were homosexual men who met the criteria for a diagnosis of AIDS as defined by the Centers for Disease Control (5). Noninvasive radiologic imaging procedures (abdominal sonography or computed tomography) were done to evaluate abdominal pain or abnormal hepatobiliary biochemical tests; and all showed dilation of the extrahepatic bile ducts, with or without intrahepatic ductal changes, in the absence of cholelithiasis or choledocholithiasis. No patient had a history of prior biliary tract disease or idiopathic inflammatory bowel disease.

All patients had endoscopic retrograde cholangiopancreatography with an Olympus JF-1T side-viewing endoscope (Olympus Corporation of America, Lake Success, New York). Prophylactic antibiotics were given before and after each procedure. An 8- to 13-mm papillotomy was made in each patient with an Olympus or Wilson-Cooke sphincterotome (Wilson-Cooke Medical Incorporated, Winston-Salem, North Carolina). Endoscopic biopsy samples were obtained with pinch forceps from the opened ampulla; samples were submitted in nonbacteriostatic saline for bacterial and viral culture and were fixed in 10% formalin for hematoxylin and eosin staining before light microscopy.

Results

The mean age of the eight patients was 36.9 years (range, 29 to 59). All but one were white. Biliary tract abnormalities were detected at a mean of 6.5 months after the initial diagnosis of AIDS (range, 2 to 9). Infections or neoplasms related to AIDS that were previously detected included cryptosporidiosis (seven patients), cytomegalovirus infection (six patients), *Pneumocystis carinii* pneumonia (five patients), *Mycobacterium avium* complex infection (two patients), and Kaposi sarcoma, non-Hodgkin lymphoma, and cryptococcosis (one patient each).

All patients evaluated had had moderate to severe epigastric pain or abdominal pain in the right upper quadrant, which was usually dull or colicky, nonradiating, and exacerbated by meals. Five patients noted fevers or rigors, and three had nausea and vomiting. Clinically severe bacterial cholangitis was the initial presentation in two patients. No patients were icteric, however, and none had pruritus.

Increased serum alkaline phosphatase activity was seen in all patients (mean, 720 IU/L; range, 193 to 1840). Serum aspartate (AST) or alanine aminotransferase (ALT) levels were elevated in seven of eight patients (mean AST of 142 IU/L, range of 26 to 445; mean ALT of 212 IU/L, range of 24 to 539). Total serum bilirubin levels were normal in all patients (Table 1).

▶ From the Division of Gastroenterology, Department of Medicine, and the Department of Radiology, San Francisco General Hospital; and the University of California, San Francisco; San Francisco, California.

Table 1. Clinical, Biochemical, and Histopathologic Profiles of Eight Men with the Acquired Immunodeficiency Syndrome and Papillary Stenosis and Sclerosing Cholangitis

Patient	Age	Prior AIDS-Related Conditions*	Alanine Aminotransferase†		Alkaline Phosphatase†		Interval Between Measurements	Biliary Sepsis	Pathogen on Biopsy
			Before ERCP	After ERCP	Before ERCP	After ERCP			
	yrs		←		*IU/L*		→ *d*		
1	40	PCP, MAC, CMV	395	33	1205	699	30	No	No biopsy
2	32	PCP, CS	65	43	423	476	6	Yes‡	None
3	33	PCP, CS, CMV	79	75	246	358	19	No	None
4	33	CS	76	38	740	256	26	No	CS
5	38	PCP, MAC, CMV, CS, CC	243	56	780	186	14	No	CMV
6	29	CMV, CS, lymphoma	277	125	193	670	25	No‡	None
7	31	KS, CS, CMV	539	54	1840	397	19	Yes	CS, CMV
8	59	PCP, CS, CMV	24	43	329	389	25	No	None

* AIDS = acquired immunodeficiency syndrome; CC = cryptococcosis; CMV = cytomegalovirus; CS = cryptosporidiosis; KS = Kaposi sarcoma; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis carinii* pneumonia.

† ERCP = endoscopic retrograde cholangiopancreatography. Normal range for alanine aminotransferase is 10 to 45 IU/L and for alkaline phosphatase is 40 to 115 IU/L.

‡ Developed bacterial cholangitis 2 to 8 weeks after sphincterotomy.

Abdominal ultrasonography showed dilation of the extrahepatic common bile ducts (mean diameter, 11 mm) and intrahepatic bile ducts in all six patients examined. A distal common bile duct stricture was suspected in three of these patients. Intrahepatic duct stricturing was seen in one additional patient. Although no gallstones were seen, one sonogram showed "sludge" in the gallbladder. Likewise, computed tomography, done on four patients, disclosed dilated intrahepatic and extrahepatic biliary ducts. No periportal or peripancreatic lymphadenopathy, pancreatic head enlargement, or pancreatic masses were seen to account for the obstruction.

Endoscopic retrograde cholangiopancreatography was successfully done on all patients. The papilla of Vater appeared normal on gross examination. A single patient had small focal Kaposi sarcoma lesions in the duodenum that did not involve the papilla. Visualization of the biliary tree confirmed both intrahepatic and extrahepatic duct dilation (Figure 1). In addition, all patients showed scattered intrahepatic ducts that had focal stricturing or beading and decreased arborization and terminal "pruning" of the secondary or tertiary radicles, consistent with cholangitis. Three patients had focal stricturing of the proximal extrahepatic bile ducts. Strictures of up to 1.3 cm in length were seen in the distal common bile duct in all patients and often extended proximal to the intraduodenal segment. Endoscopic papillotomy (8 to 13 mm) was done in all patients. Qualitatively, the papillary wall appeared thicker than normal and required prolonged, high-energy diathermy to achieve satisfactory sphincterotomy.

Transendoscopic ampullary biopsy samples were obtained in seven patients. All showed focal areas of acute and chronic inflammation. Cryptosporidia were seen adherent to ductular epithelial cells in two of the patients. Although no intraepithelial viral inclusions were seen, two specimens grew cytomegalovirus in culture, including one with concomitant histologic evidence of cryptosporidiosis. No bacterial pathogens were isolated.

After sphincterotomy, abdominal pain immediately resolved in all patients. As shown in Table 1, serum levels of alkaline phosphatase and ALT fell appreciably 6 to 30 days after the procedure in four of eight patients. Of the four patients without a favorable biochemical response, two developed gram-negative bacterial cholangitis 2 weeks and 2 months later, respectively. Both required extension of the papillotomy in addition to treatment with systemic antibiotics. Of note, however, both also had lengthy strictures of the distal common bile duct that involved the extraduodenal intrapancreatic segment, an area not accessible to endoscopic transection. The other two patients continued to improve clinically despite a rise in serum chemistry values. No patient required surgical intervention. Overall, six of eight patients having sphincterotomy had a favorable clinical response.

Four patients died during follow-up (mean, 155 days after sphincterotomy; range, 35 to 248). The causes of death were unrelated to hepatobiliary disease or the sphincterotomies. Of the four survivors (mean follow-up after sphincterotomy, 77 days; range, 15 to 192), none has noted recurrent symptoms related to the biliary tract.

Discussion

This study presents the largest series of patients with AIDS and biliary tract disease reported to date. We have described the features of papillary stenosis and sclerosing cholangitis in eight patients. Stenosis of the papilla of Vater, in both patients with AIDS (2-4) and immunocompetent hosts (6, 7), may produce a clinical syndrome of abdominal pain, nausea and vomiting, biochemical evidence of cholestasis, and, rarely, fevers, chills, or jaundice. Radiologically, dilated extrahepatic bile ducts, and often intrahepatic bile ducts, are seen proximal to the smoothly tapered distal common bile duct. Surgical sphincteroplasty or choledochoenterostomy has been largely supplanted by endoscopic sphincterotomy for therapeutic decompression (6-10).

In the absence of gallstone disease and prior episodes of suppurative cholangitis, the proximal bile ducts in patients with papillary stenosis are usually smooth and uniformly dilated. In contrast, sclerosing cholangitis produces focal irregularities of the intrahepatic and extrahepatic

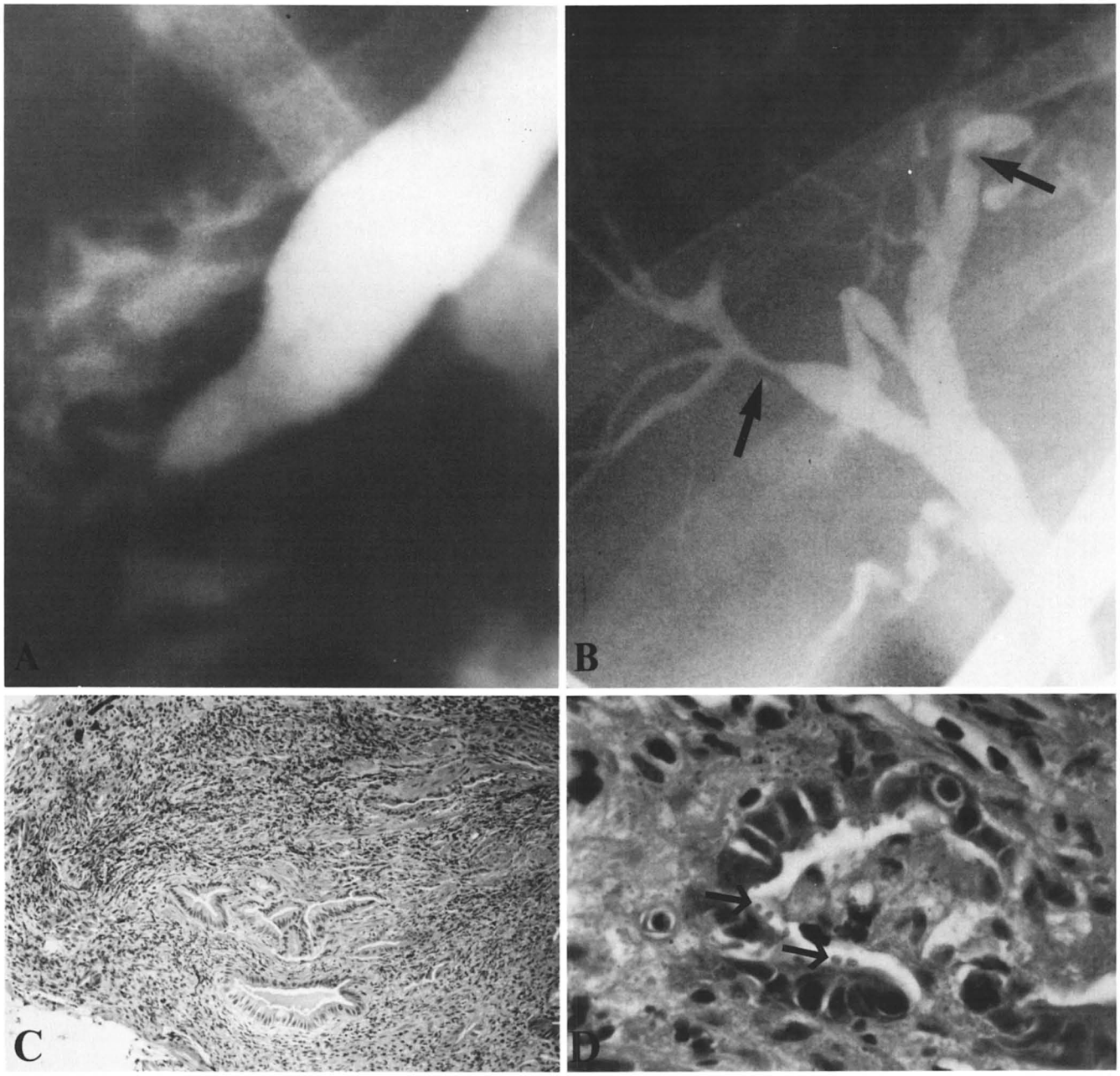

Figure 1. Ductal abnormalities seen on endoscopic cholangiography and biopsy. **Figure 1A.** Markedly dilated common bile duct with distal stricture, suggestive of papillary stenosis. **Figure 1B.** Intrahepatic biliary radicles with focal stricturing (*arrows*), decreased arborization, and terminal branch pruning, typical of sclerosing cholangitis. **Figure 1C.** Columnar-cell-lined ampullary glands in a background of predominantly chronic inflammatory cells (hematoxylin and eosin; original magnification, × 125). **Figure 1D.** Glandular epithelium with adherent cryptosporidia (*arrows*) on lumenal surface (hematoxylin and eosin; original magnification, × 640).

ducts, consisting of short strictures with intervening segments of normal or increased caliber. Intrahepatic ducts may also display decreased arborization and pruning of the terminal branches. Because these lesions are often diffusely distributed throughout the biliary tree, both surgical and endoscopic decompression procedures are technically difficult, and symptoms in patients often progress from abdominal pain, jaundice, and pruritus to portal hypertension and hepatic failure due to secondary biliary cirrhosis (11-13).

The eight patients presented herein appeared to have features of both papillary stenosis and sclerosing cholangitis. Abdominal pain, nausea and vomiting, and fever were the commonest presenting symptoms, although clinical cholangitis was the initial manifestation in two patients. The pattern of liver enzyme abnormalities was primarily cholestatic, with marked increases of serum alkaline phosphatase activity (mean, 720 IU/L) and less severe changes in aminotransferase values. Total serum bilirubin levels were normal, and clinical icterus was universally absent on initial evaluation. The latter findings suggest that the obstructive process was incomplete.

Although abdominal sonography or computed tomography provided initial evidence of ductal abnormalities, endoscopic cholangiography showed the precise anatomical irregularities. Moreover, endoscopic sphincterotomy was the sole treatment needed, as prompt symptomatic relief followed sphincterotomy in all eight patients. However, two patients subsequently (2 to 8 weeks later) developed suppurative cholangitis possibly related to the prior papillotomies. Of note, the stenosis of the distal common bile duct in these two patients extended beyond the intramural (intraduodenal) segment, a contraindication to complete endoscopic transection because of the high risk for perforation.

The cause of the ductal abnormalities is, as yet, uncertain. In patients without immunodeficiency, papillary stenosis is usually associated with scarring after surgery, inflammation or fibrosis from stone passage, ductal carcinoma, or external compression from chronic pancreatitis or periampullary diverticula. A subset of patients have idiopathic papillary dyskinesia or spasm (10, 14). Similarly, sclerosing cholangitis has been associated with surgical trauma, biliary calculi, suppurative cholangitis, congenital anomalies, or malignancy. Primary sclerosing cholangitis has been detected in some patients with idiopathic inflammatory bowel disease (particularly ulcerative colitis) and thyroid disease (11-13). These conditions were notably absent in the patients we examined.

Opportunistic infection provides the most likely explanation for our findings. Both cytomegalovirus and cryptosporidia have been found in the bile, gallbladder, and ductal mucosa of patients with AIDS. Furthermore, the previously reported cases of distal common bile duct obstruction, with or without intrahepatic ductular abnormalities, occurred in patients with AIDS infected with cryptosporidia or cytomegalovirus (1-4). In our series, all patients had documented extrabiliary infection with cryptosporidia (seven patients), cytomegalovirus (six patients), or both (five patients). Ampullary biopsy samples were diagnostic for cryptosporidiosis or cytomegalovirus infection in three patients, including one biopsy sample that yielded both organisms. Because evaluations of endoscopic ampullary biopsy in this condition have not, to our knowledge, been previously reported, it is unclear whether a low diagnostic accuracy is to be expected. Sampling error or the thermal effects (from sphincterotomy) on ductal tissue may have reduced the likelihood of isolating an etiologic agent.

We speculate that either cytomegalovirus or cryptosporidia induced an inflammatory response resulting in viral or coccidial cholangitis. Edema, spasm, and fibrosis likely account for the radiologic findings. Symptoms and biochemical abnormalities may reflect incomplete biliary obstruction.

In summary, papillary stenosis and sclerosing cholangitis are unappreciated complications of AIDS, and their clinical and radiologic features have only recently been recognized in these patients. Cytomegalovirus, cryptosporidia, or both are likely etiologic agents, although confirmatory studies are warranted. Significant morbidity from abdominal pain, nausea and vomiting, or superimposed bacterial cholangitis may occur. Most patients will respond favorably to biliary decompression achieved with endoscopic papillotomy.

ACKNOWLEDGMENTS: The authors thank Rosanne Sharp, Lee Stressenger, and Thomas Weber for technical and editorial assistance.

Grant support: in part by training grant AM 07007 from the National Institutes of Health.

▶ Requests for reprints should be addressed to John P. Cello, M.D.; Division of Gastroenterology, San Francisco General Hospital, 1001 Potrero Avenue, Room 3C-19; San Francisco, CA 94110.

References

1. Kavin H, Jonas RB, Chowdhury L, Kabins S. Acalculous cholecystitis and cytomegalovirus infection in the acquired immunodeficiency syndrome. *Ann Intern Med.* 1986;**104**:53-4.
2. Pitlik S, Fainstein V, Rios A, Guarda L, Mansell PWA, Hersh EM. Cryptosporidial cholecystitis [Letter]. *N Engl J Med.* 1983;**308**:967.
3. Pitlik S, Fainstein V, Garza D, et al. Human cryptosporidiosis: spectrum of disease: report of six cases and review of the literature. *Arch Intern Med.* 1983;**143**:2269-75.
4. Margulis SJ, Honig CL, Soave R, Govoni AF, Mouradian JA, Jacobson IM. Biliary tract obstruction in the acquired immunodeficiency syndrome. *Ann Intern Med.* 1986;**105**:207-10.
5. Fauci AS, Macher AM, Longo DL, et al. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med.* 1984;**100**:92-106.
6. Shingleton WW, Gamburg D. Stenosis of the sphincter of Oddi. *Am J Surg.* 1970;**119**:35-7.
7. Nardi G. Papillitis and stenosis of the sphincter of Oddi. *Surg Clin North Am.* 1973;**53**:1149-60.
8. Koch H, Rosch W, Schaffner O, Demling L. Endoscopic papillotomy. *Gastroenterology.* 1977;**73**:1393-6.
9. Liguory C, Loriga P. Endoscopic sphincterotomy: analysis of 155 cases. *Am J Surg.* 1978;**136**:609-13.
10. Geenen JE, Toouli J, Hogan WJ, et al. Endoscopic sphincterotomy: follow-up evaluation of effects on the sphincter of Oddi. *Gastroenterology.* 1984;**87**:754-8.
11. Longmire WP Jr. When is cholangitis sclerosing? *Am J Surg.* 1978;**135**:312-20.
12. Weisner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology.* 1980;**79**:200-6.
13. Dickson ER, LaRusso NF, Weisner RH. Primary sclerosing cholangitis. *Hepatology.* 1984;**4**(1 suppl): 33S-5S.
14. Toouli J, Roberts-Thomson IC, Dent J, Lee J. Manometric disorders in patients with suspected sphincter of Oddi dysfunction. *Gastroenterology.* 1985;**88**(5 pt 1): 1243-50.