0002-9270/86/8111-1068
THE AMERICAN JOURNAL OF GASTROENTEROLOGY

Vol. 81, No. 11, 1986
Printed in U.S.A.

# Cytomegalovirus Cholangitis in a Homosexual Man with Acquired Immune Deficiency Syndrome

**Farooq P. Agha, M.D., F.A.C.G., Timothy T. Nostrant, M.D., Gerald D. Abrams, M.D., Mary Mazanec, M.D., Lisa Van Moll, M.D., and Jorge J. Gumucio, M.D.**

*Department of Radiology, Internal Medicine, and Pathology, University of Michigan Hospitals and Medical School, Ann Arbor, Michigan*

**A 29-yr-old white homosexual man with acquired immune deficiency syndrome presented initially with right upper quadrant pain and progressive cholestasis. Diffuse mucosal irregularities were seen at endoscopic retrograde cholangiography. Histopathological examination of the gallbladder and wedge liver biopsy showed evidence of cytomegalovirus infection. A repeat endoscopic retrograde cholangiography for persistent symptoms of right upper quadrant pain and cholestasis showed progressive mucosal irregularities of the intra- and extrahepatic bile ducts consistent with progressive cholangitis. Subsequently the patient developed evidence of disseminated infection and died. Postmortem examination revealed histologic features of cytomegalovirus infection in lungs, pancreas, small bowel, adrenal glands, and liver. Immunohistochemical staining of liver confirmed the presence of cytomegalovirus infection of the biliary duct system.**

## INTRODUCTION

The acquired immune deficiency syndrome (AIDS) is characterized by recurrent viral and bacterial infections which involve multiple organ systems (1–8). We report a case of a homosexual man with documented cytomegalovirus (CMV) infection involving the biliary tract and gallbladder.

## CASE REPORT

A 29-yr-old white male homosexual presented in November 1983, with a 2-wk history of increasing right upper quadrant pain and weight loss. Initially, the pain was intermittent but eventually became continuous. The pain had no relation to food or bowel movements. The patient's past history included extensive homosexual exposure (over 1000 contacts), hepatitis-B infection, and shigellosis. Initial physical examination and laboratory studies were unremarkable except for mild right upper quadrant tenderness and a SGPT of 46 IU (normal 1–33 IU/L). An oral cholecystogram revealed nonvisualization of the gallbladder and ultrasonography showed no gallstones or biliary dilatation. The pain decreased during hospitalization and the patient was discharged.

Two weeks after discharge the patient began to complain of night sweats and daily temperature spikes to 101°F. Because of continued weight loss, fever, and increasing right upper quadrant pain, the patient was readmitted in January 1984. Repeat physical examination revealed continued right upper quadrant tenderness and cervical lymphadenopathy. Liver chemistries were normal except for a progressive increase in alkaline phosphatase from 108 (normal 30–96 IU/L) to 160 IU. Cultures of blood, stool, urine were negative for pathogenic bacteria or viruses, and biopsy of the cervical lymph node revealed no pathological abnormality. Abdominal computed tomography showed mild common bile duct dilatation. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated dilatation of both the intrahepatic and extrahepatic bile ducts with diffuse mucosal irregularities (Fig. 1). Because of increasing right upper quadrant pain and fever, a pre-

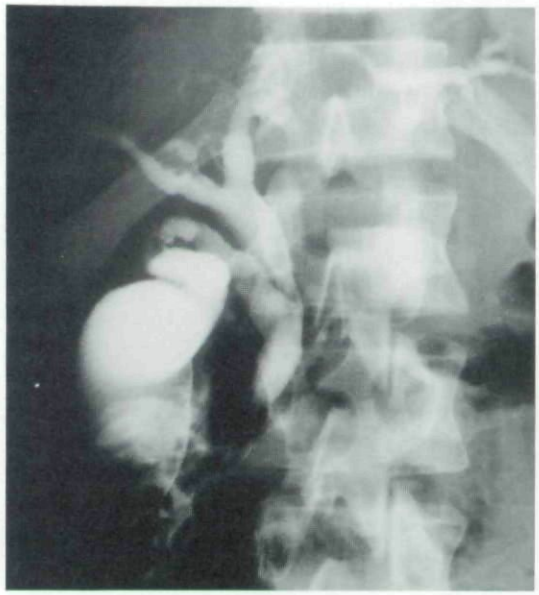

FIG. 1. ERCP—January 1984. ERCP shows diffuse mucosal irregularity of the intra- and extrahepatic bile ducts. There is nonobstructive dilatation of common bile duct, cystic duct, and both main hepatic ducts. The findings are consistent with severe ulcerative cholangitis.

*Received Oct. 18, 1985; revised May 19, 1986; accepted June 25, 1986.*

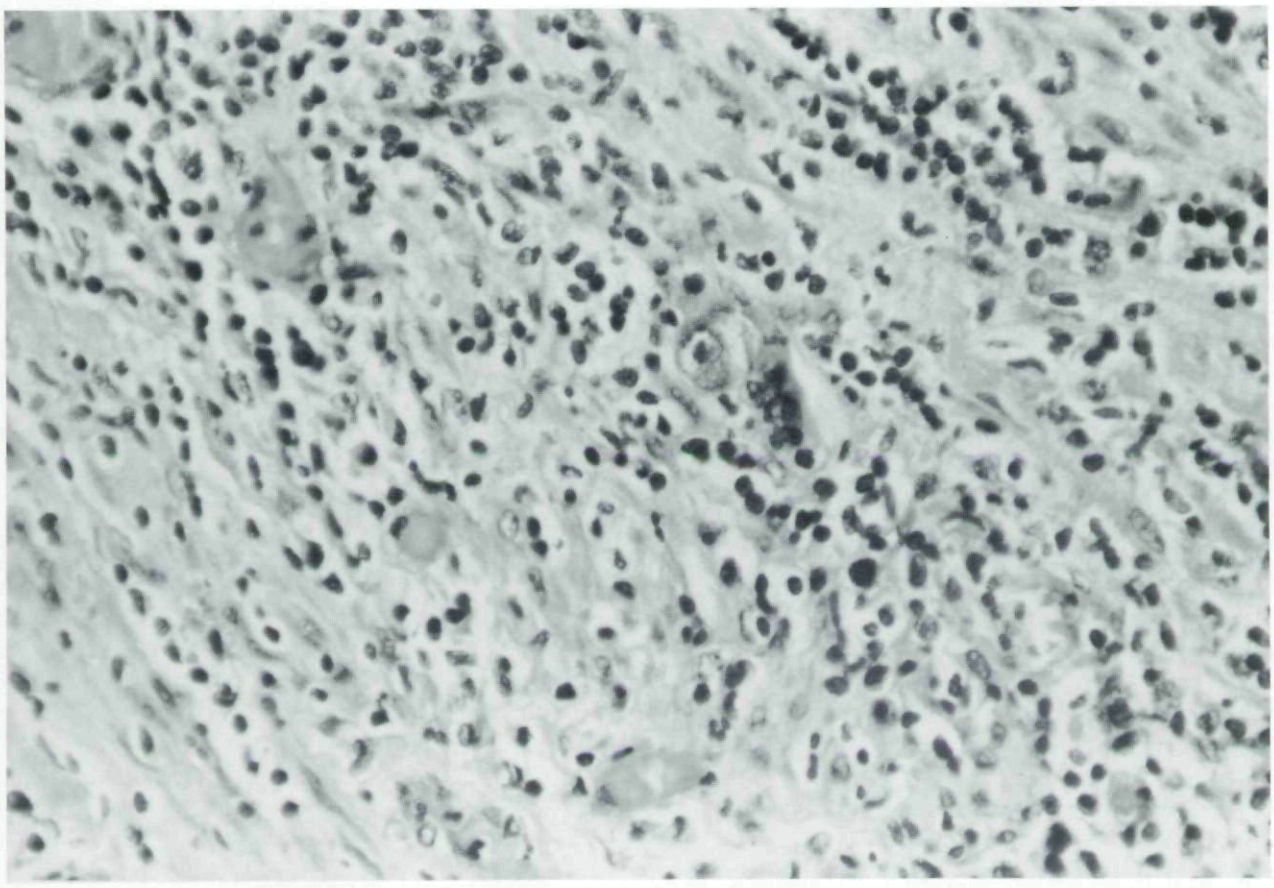

FIG. 2. Photomicrograph of surgically removed gallbladder. Within the chronic inflammatory infiltrate (*right of center*) is an enlarged cell, presumably an endothelial cell with a large intranuclear inclusion (hematoxylin and eosin, ×470).

sumptive diagnosis of acute cholecystitis was made and laparotomy was performed. An inflamed gallbladder was removed and a wedge liver biopsy was obtained. Histopathological examination of the gallbladder revealed severe acute and chronic cholecystitis with occasional CMV inclusions apparently in endothelial cells (Fig. 2). Liver biopsy revealed periportal inflammation with rare hepatocytes containing large intranuclear inclusions.

Right upper quadrant pain and weight loss continued postoperatively. T cell studies showed "helper-suppressor T cell ratio of 0.1." AIDS was suspected and the patient was transferred to the University of Michigan Hospital in March 1984. Admission physical examination revealed cachexia, diffuse lymphadenopathy, temperature to 102°F, dehydration, and hepatomegaly. Because of persistent gastrointestinal bleeding, diarrhea, and a decreased hematocrit, the patient underwent upper gastrointestinal endoscopy which revealed diffuse Candida esophagitis, and extensive erosive disease in the gastric antrum and proximal duodenum. Duodenal biopsy and aspirates as well as stool cultures were positive for CMV, *Giardia lamblia, Clostridum difficile,* and cryptosporidium. Colonoscopy revealed focal ulcers. No CMV inclusions were found in the colonic biopsies. IgM antibodies to cytomegalovirus rose from a titer of 1:8 to 1:64. Titers to herpes virus 1 and 2 *Toxoplasma gondii,* Epstein-Barr virus, and rubella were negative. Because of the previous ERCP findings, persistent abdominal pain, and increasing cholestasis (alkaline phosphatase 369 IU), a repeat ERCP was performed (Fig. 3). Progressive narrowing of the intra-

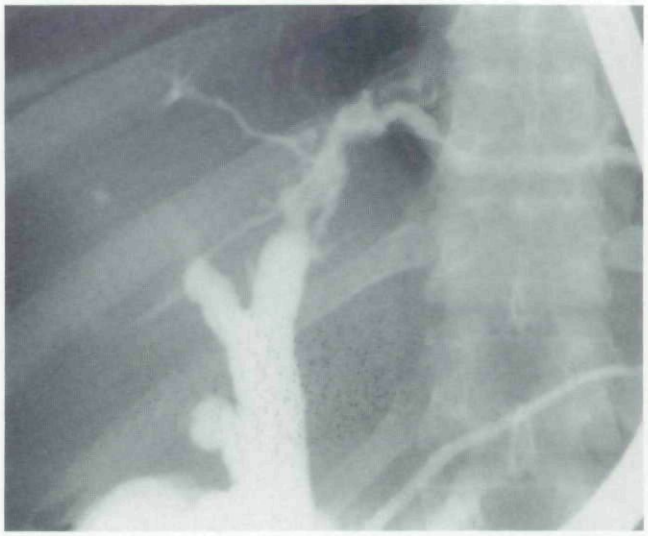

FIG. 3. ERCP—March 1984. Progressive mucosal irregularities of the intra- and extrahepatic bile ducts are present. The intrahepatic bile ducts have a "pruned" appearance.

hepatic bile ducts was noted. Increased narrowing and mucosal irregularities were also demonstrated in the extrahepatic bile ducts. The patient's fever and abdominal pain spontaneously resolved and he was discharged.

From April 1984, to September 1984, the patient's course was complicated by recurrent right upper quadrant pain, intermittent fever, incapacitating diarrhea secondary to cryptosporidiosis, and pneumonia secondary to *Pneumocystis carinii.* On September 27, 1984, the patient was readmitted because of persistent cough and cyanosis. Chest x-ray revealed progressive pulmonary consolidation. Bronchial washings revealed cells with large intranuclear inclusions indicative of CMV infection as well as *Aspergillus hyphae* and yeast. Respiratory function deteriorated despite intensive treatment, and the patient died on October 3, 1984.

Autopsy revealed histological features of extensive CMV infection of the lungs, pancreas, small bowel, and adrenal glands. Gross inspection of the liver demonstrated moderate hepatomegaly and steatosis. Although no gross abnormality of the biliary ducts was noted there was a moderate lymphoplasmocytic infiltrate and slight sclerosis in many portal tracts. Although postmortem autolysis obscured some cellular detail, a large intrahepatic bile duct near the hilum of the liver was found to be ulcerated with a chronic inflammatory reaction in the wall. In the immediately adjacent smaller bile ducts, many CMV inclusions were evident. In smaller portal tracts scattered throughout the liver, CMV inclusions were encountered, sometimes apparently within endothelial cells, but often clearly within epithelial cells of small ducts and neocholangioles (Fig. 4). Immunohistochemical staining for CMV and herpes virus was performed on sections of liver obtained at autopsy. Formalin-fixed, paraffin-embedded tissue was stained using the avidin-biotin peroxidase method (9). Antibody (goat) to CMV was obtained from Polyscience, Warrington, PA; and antibody (rabbit) to herpes simplex virus I was obtained from Dako, Santa Barbara, CA. Control sections were prepared in paralleled using normal goat serum. Immunoperoxidase staining for CMV was strongly positive in many small ducts, neocholangioles, and endothelial cells corresponding to the cytopathic changes (Fig. 5). Staining

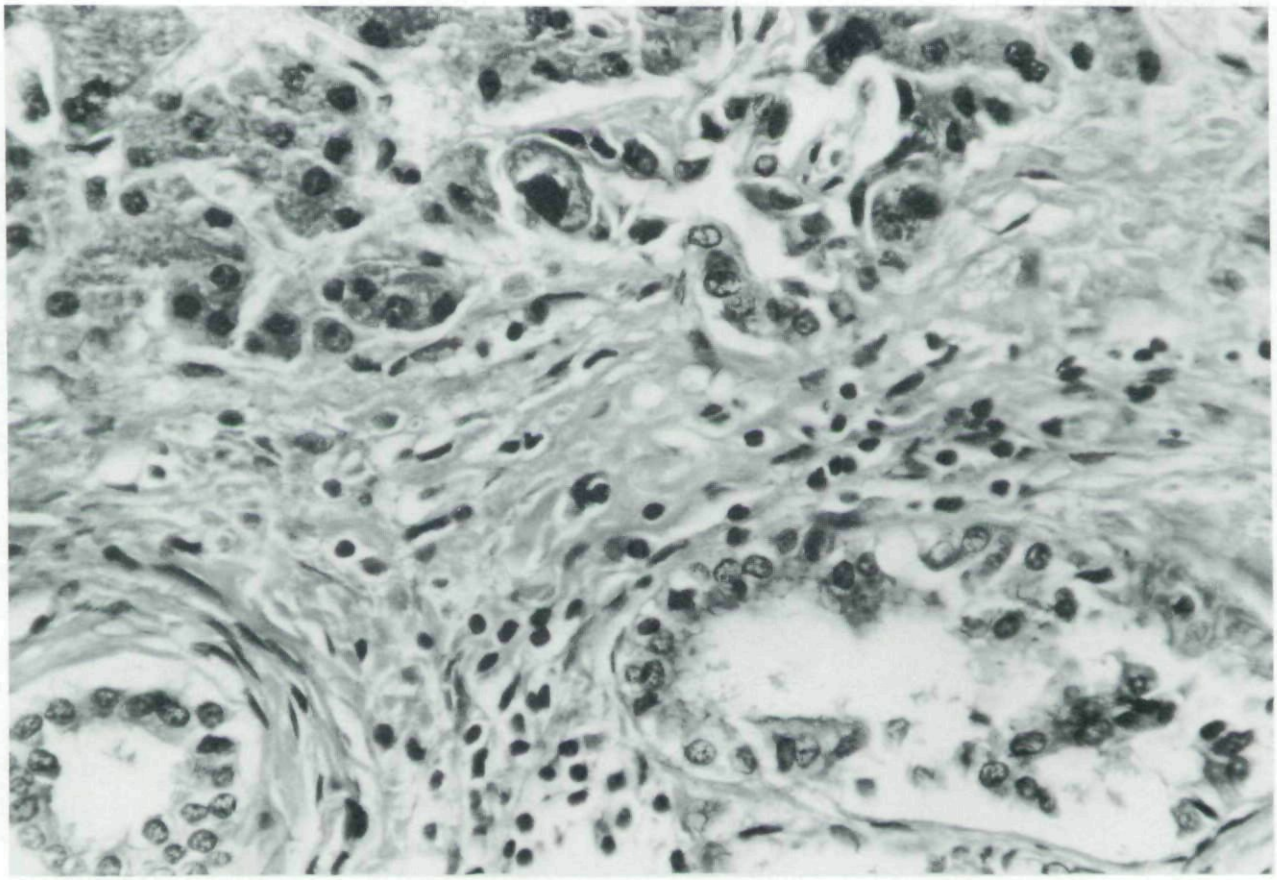

FIG. 4. Photomicrograph of autopsy specimen of liver. The portal area shows mild chronic inflammation and sclerosis. Several of the ductal epithelial cells at the *top* of the figure, to the *right of center*, are enlarged. One cell at the 9 o'clock position and one at the 12 o'clock position have intranuclear inclusions. A cell at the 3 o'clock position also has intracytoplasmic inclusion material (hematoxylin and eosin, ×470).

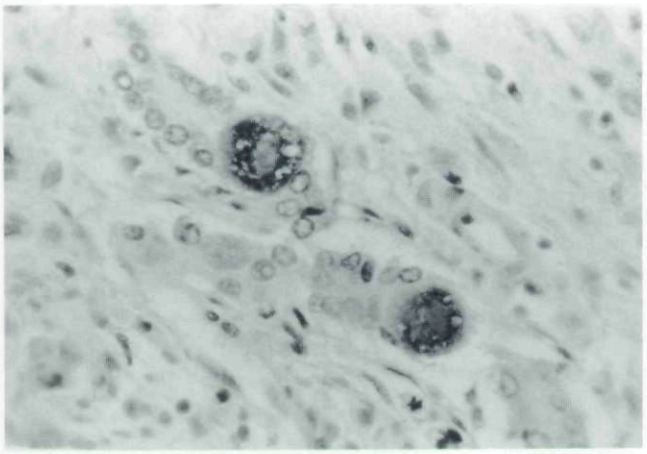

FIG. 5. Photomicrograph of immunoperoxidase stain of liver for CMV antigen. In each of the two bile ducts pictured, an enlarged epithelial cell is strongly positive (×470).

for herpes virus was negative. The overall histopathological picture was thus indicative of extensive CMV infection of the biliary ductal system.

## DISCUSSION

CMV infection is common in AIDS patients. Infection of the gastrointestinal tract (2, 4, 6, 7, 10–20) and the liver (21–25) by CMV has been previously reported. Once established, CMV frequently persists for the life of the patient, as it did in this case (1).

The pathogenesis of CMV-associated gastrointestinal disease is controversial (13–17). Although CMV is frequently seen in association with ulcers in both the upper and lower gastrointestinal tract, a mechanism for CMV-induced epithelial damage has not been demonstrated. Foucar *et al.* (16) believe that CMV produces a local vasculitis which causes the mucosal damage. On the other hand, whether CMV causes damage or infects already damaged mucosa has not been conclusively proven. The possibility that this case of cholangitis represents a secondary CMV infection with the primary pathogenic organism being HTLV III, the presumed causative agent of AIDS, cannot be dismissed. However, the presence of CMV in association with the damaged biliary tract, a rising IgM CMV titer, and positive cultures for CMV from multiple organ sites suggest a significant pathogenetic role for this agent in this patient.

Although the initial transaminase and alkaline phosphatase elevations in this patient were thought to represent a nonspecific response to systemic infection or CMV hepatitis, progressive pain and fever prompted ERCP, which documented severe cholangitis. Furthermore, the timing of pain and fever was closely correlated with increasing alkaline phosphatase. Progressive biliary tract destruction was further documented by repeat ERCP and this paralleled the patient's deteriorating course.

In summary, a case of CMV cholangitis in a patient with AIDS is reported. This diagnosis should be considered in patients with AIDS who present with fever, right upper quadrant pain, and evidence of increasing cholestasis.

Reprint requests: Dr. Farooq P. Agha, Department of Diagnostic Radiology, Evanston Hospital, Northwestern University, 2650 Ridge Avenue, Evanston, IL 60201.

## REFERENCES

1. Bett RF, Hanshaw JB. Cytomegalovirus (CMV) in the compromised host. Ann Rev Med 1977;28:103–10.
2. Freeman HJ, Shnitka TK, Piercey JRA, et al. Cytomegalovirus infection of the gastrointestinal tract in a patient with late onset immunedeficiency syndrome. Gastroenterology 1977;73:1397–403.
3. Durack DT. Opportunistic infections and Kaposi's sarcoma in homosexual men. N Engl J Med 1981;305:1465–7.
4. Drew WL, Miner RC, Sand M, et al. Prevalence of cytomegalovirus infection in homosexual men. J Infect Dis 1981;143:188–92.
5. Mildvan D, Mathur U, Enlow RW, et al. Opportunistic infections and immunedeficiency in homosexual men. Ann Intern Med 1982;96:700–4.
6. Gottlieb MS, Groopman JE, Weinstein WM, et al. The acquired immune deficiency syndrome. Ann Intern Med 1983;99:208–10.
7. Riechert CM, O'Leary TJ, Levens DL, et al. Autopsy pathology in the acquired immunedeficiency syndrome. Am J Pathol 1983;112:357–82.
8. Hill CA, Harle TS, Mansell PWA. The prodrome, kaposi sarcoma, and infections associated with acquired immunedeficiency syndrome: radiologic findings in 39 patients. Radiology 1983;149:393–9.
9. Lloyd RV, Landefeld TD, Maslar I, et al. Diethylstilbestrol inhibits tumor growth and prolactin production in rat pituitary tumors. Am J Pathol 1985;118:379–86.
10. Brennan RO, Durack DT. Gay compromise syndrome. Lancet 1981;2:1338–9.
11. Weinstein L, Edelstein SM, Madara JL, et al. Intestinal cryptosporidiosis complicated by disseminated cytomegalovirus infection. Gastroenterology 1981;81:584–91.
12. Gertler SL, Pressman J, Price P, et al. Gastrointestinal cytomegalovirus infection in a homosexual man with severe acquired immune deficiency syndrome (AIDS). Gastroenterology 1983;85:1403–6.
13. Rosen P, Armstrong D, Rice N. Gastrointestinal cytomegalovirus infection. Arch Intern Med 1973;132:274–6.
14. Onge GS, Bezahler GH. Giant esophageal ulcer associated with cytomegalovirus. Gastroenterology 1982;83:127–30.
15. Goodman MD, Porter DD. Cytomegalovirus vasculitis with fatal colonic hemorrhage. Arch Pathol 1973;96:281–4.
16. Foucar E, Mukai K, Foucar K, et al. Colon ulceration in lethal cytomegalovirus infection. Am J Clin Pathol 1981;76:788–801.
17. Meiselman MS, Cello JP, Margaretten W. Cytomegalovirus colitis: report of the clinical, endoscopic and pathologic findings in two patients with the acquired immune deficiency syndrome. Gastroenterology 1985;88:171–5.
18. Spiegel JA, Schwabe AD. Disseminated cytomegalovirus infection with gastrointestinal involvement: the role of altered immunity in the elderly. Am J Gastroenterol 1980;73:40.
19. Knapp AB, Horst DA, Eliopoulos G, et al. Widespread cytomegalovirus gastroenterocolitis in a patient with acquired immunedeficiency syndrome. Gastroenterology 1983;85:1399–402.
20. Balthazar EJ, Megibow AJ, Fazzini E, et al. Cytomegalovirus

colitis in AIDS: radiologic findings in 11 patients. Radiology 1985;155:585–9.
21. Henson D. CMV hepatitis in an adult. Arch Pathol 1969;88:199–203.
22. Hanshaw JB, Betts RF, Simon G, et al. Acquired cytomegalovirus infection: association with hepatomegaly and abnormal liver function tests. N Engl J Med 1965;272:602–9.
23. Lamb SG, Stern H. Cytomegalovirus mononucleosis with jaundice as presenting sign. Lancet 1966;2:1003–6.
24. Henson D, Smith RD, Gehrke J. Nonfatal mouse cytomegalovirus hepatitis. Am J Pathol 1966;49:871–88.
25. Ruebner BH, Miyai K, Slusser RJ, et al. Mouse cytomegalovirus infection: an electron microscopic study of hepatic parenchymal cells. Am J Pathol 1964;44:799–821.