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# The Relationship of Cholangiocarcinoma with Human Immunodeficiency Virus Cholangiopathy and Cytomegalovirus Infection

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## ABSTRACT

Human immunodeficiency virus (HIV) is a worldwide disease with an increasing number of cases globally. Initially, HIV cholangiopathy was often observed among such patients but has become rare after three decades because of the availability of new treatment options and potent antiretroviral drugs. Consequently, its occurrence now suggests drug resistance or disease progression. The relationship between cholangiocarcinoma and HIV remains unclear. We report the case of a patient with high-grade dysplasia of the ductus choledochus and uncontrolled disease which was treated with potent antiviral agents and bile duct dilatation.

## LEARNING POINTS

- HIV cholangiopathy should be kept in mind in an HIV-positive patient even if they are receiving combination antiretroviral therapy (cART); endoscopic retrograde cholangiopancreatography can provide symptomatic relief.
- Once HIV cholangiopathy is detected, close follow-up for cholangiocarcinoma is required.
- Opportunistic infections can cause cholangiocarcinoma in HIV-positive patients.

## KEYWORDS

Hepatosteatosis, late-onset lipid storage myopathy, lipid storage disease

## CASE DESCRIPTION

A 62-year-old, HIV-positive, afebrile, Turkish man with chronic obstructive pulmonary disease was admitted to our hospital with jaundice and lumbar pain. He had been receiving combination antiretroviral therapy (cART) with emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg for 5 years. Blood test results showed the following: AST, 64 units/l; ALT, 378 units/l; GGT, 483 units/l; ALP, 197 units/l; total bilirubin, 6.2 mg/dl; and direct bilirubin, 3.1 mg/dl. Abdominal ultrasonography revealed dilation of the proximal bile duct (17 mm). The absence of both gallbladder sludge and stones led us to the diagnosis of HIV cholangiopathy. We therefore admitted the patient for endoscopic retrograde cholangiopancreatography (ERCP).

Magnetic resonance cholangiopancreatography (MRCP) showed an enlarged gallbladder (11 cm) and dilated intrahepatic and extrahepatic bile ducts. The choledochus and extrahepatic bile ducts were lobular and abnormal. The choledochus was 22 mm in its widest part, and no filling defect was observed. Wirsung's duct was dilated. Additionally, the left lobe of the liver was absent. The spleen size was at the upper

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limit of normal with a blunt contour. The fourth segment of the liver had a possibly metastatic lesion with minimal peripheral contrast in the arterial phase and increased contrast in the late phases. Vertebral MR revealed that the L2–L3 vertebral corpus had a nodular lesion, which may also have been a metastasis. The levels of tumour markers CA-125 and CA 19-9 were 50.7 and 37.7 U/ml, respectively. PET-CT was recommended and revealed tracer uptake at the pancreatic head duodenal intersection, D7 vertebra corpus, L2 vertebral superior endplate and in the ribs (*Fig. 1*). The liver lesion noted on the MRI did not show increased uptake.

At the same time, HIV RNA test findings were negative and the CD4 count was 64 cells/mm3. The infectious disease department diagnosed the patient with AIDS and HIV cholangiopathy. Treatment with emtricitabine and tenofovir was continued. The cytomegalovirus (CMV) DNA copy number was 534 copies/ml. No treatment was recommended.

We performed ERCP, which revealed a protruding and infiltrated papilla in a normal position. We cannulated it with a needle knife, replaced the 10 Fr pigtail stent, and performed a biopsy (*Fig. 2*). The biopsy revealed high-grade dysplasia of the duodenal papilla. Surgery was not considered because of the patient's ECOG performance status and therefore he was provided with palliative care.

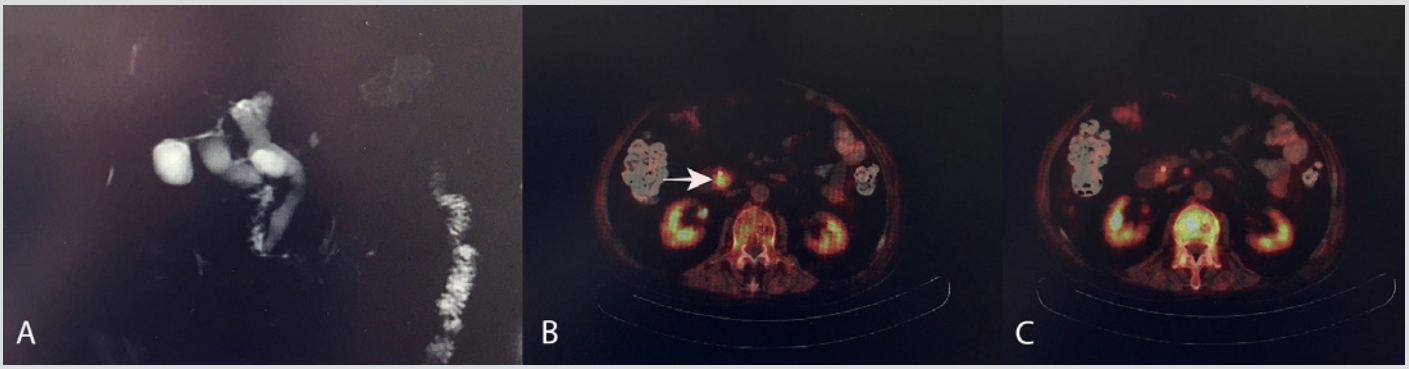


*Figure 1. A. Magnetic resonance cholangiopancreatography showing bile duct dilation. B. PET-CT scan showing tracer uptake in the papilla tumour. C. PET-CT scan showing lumbar spinal metastasis*

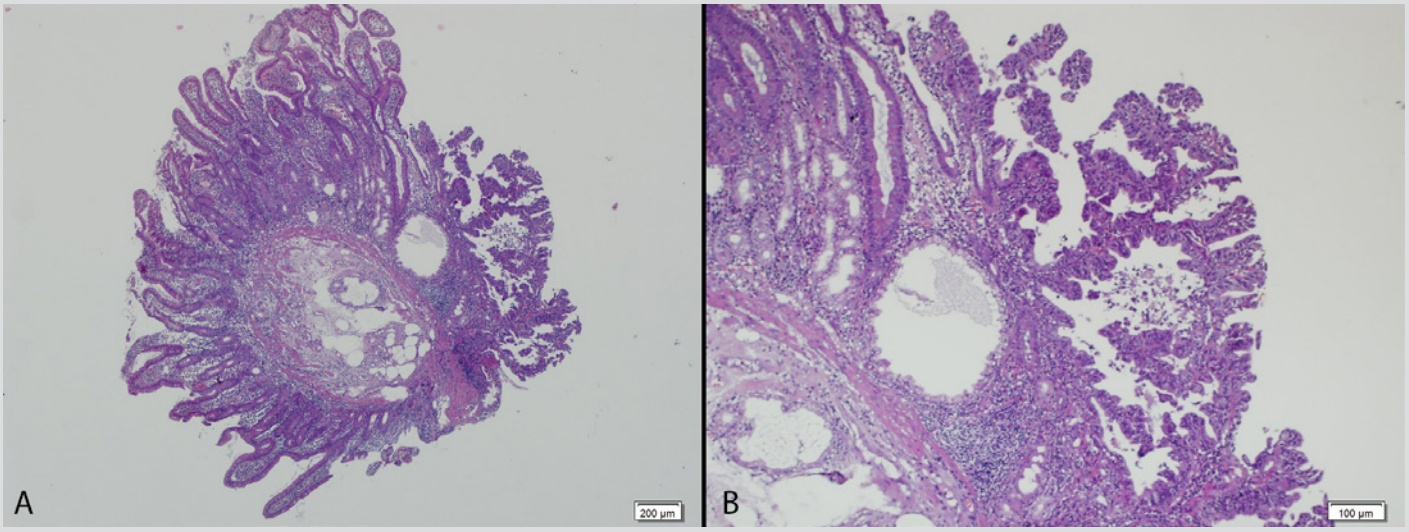


*Figure 2. A.Normal duodenal epithelium. B.High grade dysplasia (H&E, ×40)*

## DISCUSSION

HIV-associated cholangiopathy presents with right quadrant abdominal pain (90%), vomiting, nausea, fever and diarrhoea. Jaundice, which was observed in this case, is an uncommon manifestation (10%). In 20% of patients, liver function tests are normal. CD4 levels typically under 100/mm is a prognostic factor. The incidence of HIV cholangiopathy has not been determined. Papilla biopsy shows submucosal infiltration, periductal inflammation-related interstitial oedema, neutrophilic infiltration, hyperplasia in the periductal glands, and dilatation.

Ultrasound (US) is a cost-effective diagnostic modality. Common signs included choledochal dilatation (70%) and a thickened choledochal wall. A thickened gall bladder and ampulla of Vater oedema-related echogenic nodules may also be detected. Although CT may be better for intrahepatic bile duct imaging, US is more sensitive for bile duct stenosis and thickness.

Cholangiography findings are classified into four types of bile duct involvement: type 1 papillary stenosis (20%), type 2 intrahepatic sclerosing cholangitis-like pattern only (15–20%), type 3 combined papillary stenosis and intrahepatic sclerosing cholangitis (50%), and type 4 long extrahepatic bile duct stricture with or without intrahepatic involvement (15%) [1]. Differential diagnoses include primary sclerosing cholangitis, pyogenic cholangitis, fibrotic bile duct stenosis secondary to gallstones or chronic pancreatitis, acalculous cholecystitis, and cholangiocarcinoma. Although symptomatic healing occurs in 90% of patients, sphincterotomy and ursodeoxycholic acid are treatment options.

Chronic bile duct inflammation causes dysplasia and promotes cholangiocarcinoma [2]. HIV infection, although uncommon, also carries a risk for cholangiocarcinoma [3]. Infections caused by different opportunistic pathogens are common. *Cryptosporidium parvum* is the most frequently isolated pathogen in patients with HIV cholangiopathy (20–57%) [4]. This induces apoptotic cell death in cholangiocytes and can cause autonomic nerve damage in the intestine, Oddi dysfunction and papillary stenosis.

The next most commonly isolated pathogen is CMV (10–20%). CMV is an opportunistic pathogen that causes gastrointestinal tract infection in HIV-positive patients. Although its carcinogenic pathogenicity remains unclear, suspected malignancies include colon carcinoma and cholangiocarcinoma. This infection mostly occurs in the colon–rectum, small intestine, stomach and oesophagus. It causes primary sclerosing cholangitis-like syndrome with interlobular bile duct destruction.

Microsporidia and *Enterocytozoon bieneusi* are other pathogens which have been isolated. The role of *Isospora* and *Histoplasma capsulatum* is still unclear. Unfortunately, antimicrobial therapy against cytomegalovirus or other pathogens is ineffective [5].

In conclusion, even with combination antiretroviral therapy (cART), clinicians must consider the possibility of HIV cholangiopathy. Importantly, clinicians should closely follow-up patients for neoplasia. Laboratory parameters and clinical findings can help with disease management. ERCP and medical treatment provide symptomatic benefits. Moreover, early detection prolongs survival.

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