INTERNAL MEDICINE

□ CASE REPORT □

Progressive HIV-associated Cholangiopathy in an HIV Patient Treated with Combination Antiretroviral Therapy

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Abstract

We herein describe a case of progressive human immunodeficiency virus (HIV)-associated cholangiopathy despite normalization of laboratory parameters, which had indicated liver dysfunction, after the initiation of combined anti-retroviral therapy (cART). HIV-associated cholangiopathy remains important as a differential diagnosis of bile duct disorders, although it is considered to be a rare disease in the era of cART. Magnetic resonance cholangiopancreatography could thus be a powerful tool for the diagnosis and follow-up of this disease.

Key words: AIDS, HIV, cholangiopathy, MRCP, ERCP

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Introduction

Human immunodeficiency virus (HIV)-associated cholangiopathy is a biliary obstruction resulting from benign stricture of the biliary tract in patients with advanced acquired immune deficiency syndrome (AIDS) (1). The biliary tract is a frequent site of infection in patients with AIDS, and this complication was estimated to occur in up to 26% of patients with AIDS in the era before combined anti-retroviral therapy (cART) (2). Indeed, the symptoms of biliary involvement may be relatively mild, potentially leading to an underestimation of the prevalence of this disease (3). Although the etiology of this disease remains unclear, it is believed to occur in association with various opportunistic infections, such as cytomegalovirus, *Cryptosporidium spp*., and *Giardia* (4, 5). However, bile samples, including duodenal fluid obtained during upper gastrointestinal endoscopy or endoscopic retrograde cholangiopancreatography (ERCP), are not always positive for the causative pathogen (6). It is therefore impossible to rule out this complication merely because no pathogens are detected in fluid samples from the bile duct. Furthermore, an association between HIV-associated cholangiopathy and cholangiocarcinoma has been suggested, however, there have been few reports on the course of its development after the initiation of cART. Therefore, a timely diagnosis and careful follow-up are important for HIV-associated cholangiopathy.

We herein report an asymptomatic case of prolonged and progressive HIV-associated cholangiopathy, showing a further focal dilatation in an intrahepatic bile duct and persistent pruned-tree appearance, similar to the findings of primary sclerosing cholangitis, after the initiation of cART.

Case Report

A 37-year-old Japanese man, who has sex with men, was admitted to our hospital in 2011 presenting with neurosyphilis, pneumococcal pneumonia, and HIV infection. On admission, the serum aspartate aminotransferase (AST) concentration was 95 U/L, alanine aminotransferase (ALT) was 44 U/L, alkaline phosphatase (ALP) was 418 U/L, lactate dehydrogenase (LDH) was 1,205 U/L, and total bilirubin (T-bil) was 0.8 mg/dL. His CD4 cell count was 9 cells/μL and HIV-1 viral load was 1.7×10^7/mL. He had successfully accomplished both antibacterial treatments for neurosyphilis

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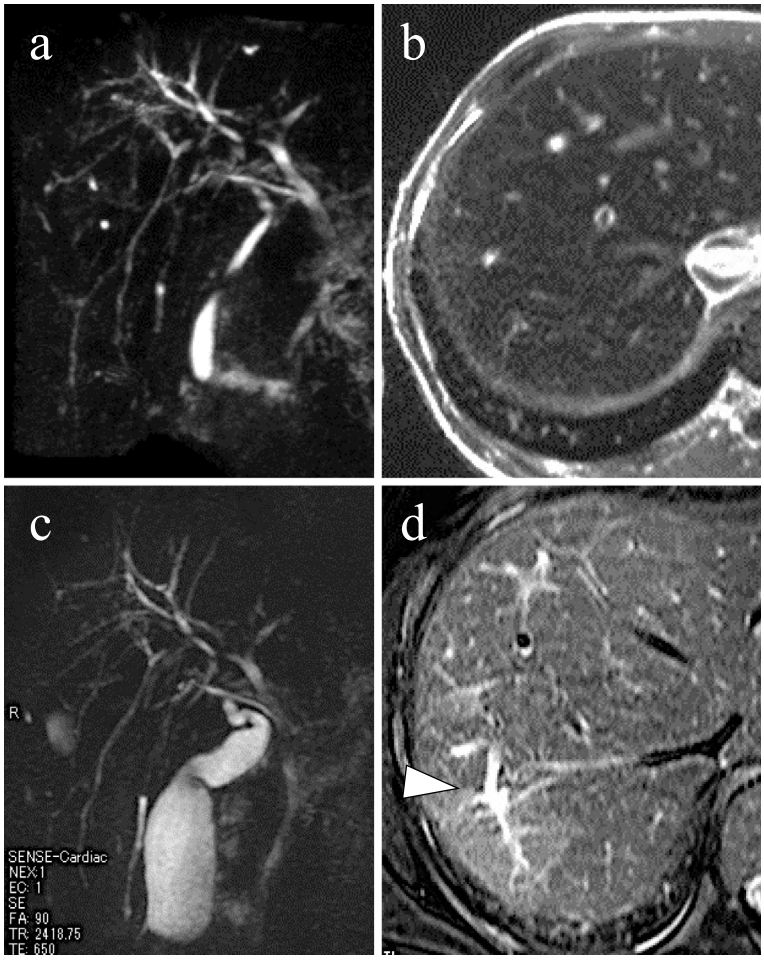

Figure 1. **Magnetic resonance imaging shows an intrahepatic bile duct stricture and pruned-tree appearance, mainly in the anterior segment of the right hepatic lobe (a, b). Magnetic resonance imaging at 15 months after the initiation of cART shows further focal dilatation in the intrahepatic bile duct (arrowhead) (c, d).**

and pneumococcal pneumonia, and his symptoms subsequently disappeared. However, the elevation of hepatic and biliary enzymes persisted despite no abnormality on an abdominal physical examination.

Although we performed additional examinations for prolonged liver dysfunction with ultrasonography (US) and contrasted-enhanced computed tomography (CT), no abnormalities were detected in the liver or other abdominal organs. Serological results for viral hepatitis were negative, and he had no history of drug use or alcoholism. Tests for serum autoantibodies, including antinuclear antibodies, anti-smooth muscle antibody, and antineutrophil cytoplasmic antibody, were negative. Magnetic resonance cholangiopancreatography (MRCP) revealed an intrahepatic bile duct stricture and pruned-tree appearance, mainly in the anterior segment of the right hepatic lobe, indicating sclerosing cholangitis (Fig. 1a and b) (1). No DNA fragments of protozoa, such as *Cryptosporidium* spp., *Giardia intestinalis*, or *Entamoeba* spp., were amplified from the duodenal fluid and stool samples (2). Cytomegalovirus DNA also tested negative in the stored frozen plasma samples obtained at the patient's initial referral to our hospital.

Given these findings, the patient's liver dysfunction was suspected to be HIV-associated cholangiopathy. He was started on a cART regimen of tenofovir, emtricitabine, and darunavir according to Japan's national protocol for AIDS therapy. The HIV viral load became undetectable after 4 months of therapy, and the CD4 cell count increased to over 200 cells/μL within 2 months of cART initiation (Fig. 2). Following the increase in the CD4 cell count, the patient's hepatic and biliary enzyme levels normalized immediately (Fig. 2). The elevation of T-bil was not observed in his clinical course. Therefore, we eventually diagnosed the patient's liver dysfunction to be HIV-associated cholangiopathy. Follow-up MRCP performed at 15 months after the initiation of cART showed further focal dilatation in an intrahepatic bile duct, with a persistent pruned-tree appearance, similar to findings in primary sclerosing cholangitis (Fig. 1c and d). Thereafter, the cART regimen was changed from darunavir to raltegravir to avoid any adverse effects from darunavir due to prolonged administration.

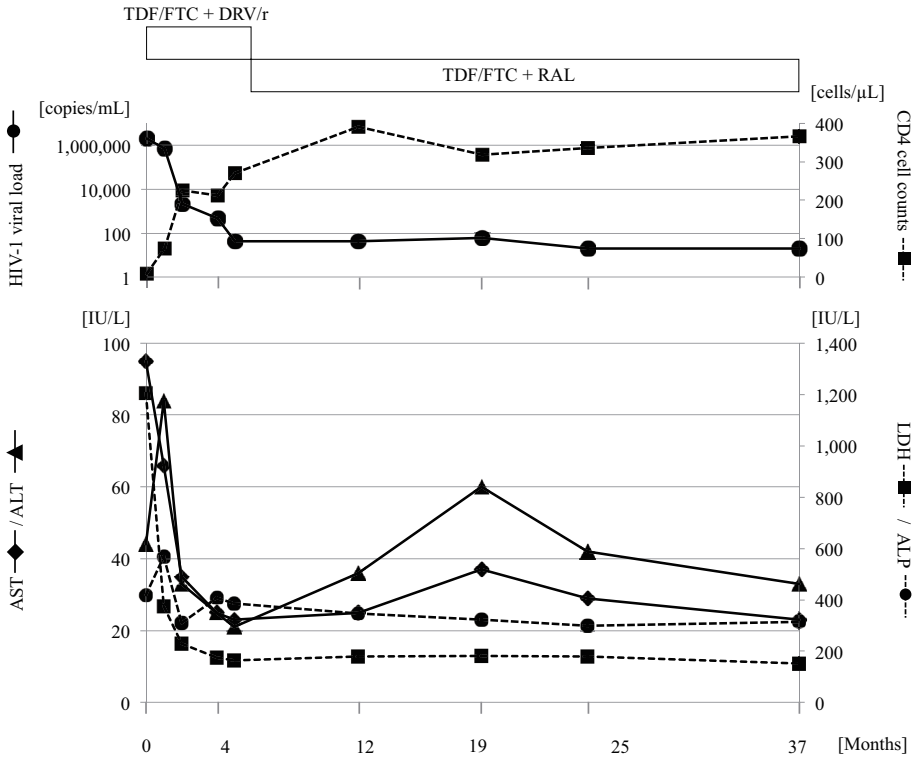

Figure 2. **The clinical course of laboratory findings after the initiation of cART. The time-dependent levels of HIV-1 viral load and CD4 cell count (upper panel) and AST, ALT, ALP and LDH (lower panel) are shown. After the initiation of cART, the AST, ALT, ALP, and LDH levels returned to within the normal ranges.**

Discussion

HIV-associated cholangiopathy is categorized into the following four types according to the ERCP findings: Type I, papillary stenosis (20% of cases); Type II, intrahepatic sclerosing cholangitis-like pattern alone (15-20%), Type III: combined papillary stenosis and intrahepatic sclerosing cholangitis (50%); and Type IV, long extrahepatic bile duct stricture with or without intrahepatic involvement (15%) (7). Although some reports of HIV-associated cholangiopathy have included asymptomatic patients, its most common manifestation is right upper quadrant abdominal pain of biliary origin or pancreatitis (8). Devarbhavi et al. demonstrated that sphincterotomy for papillary stenosis due to HIV-associated cholangiopathy, (i.e., the most common feature of this disease) could resolve the patient's symptom of severe abdominal pain (8). Therefore, the presence of stenosis at the ampulla of Vater might lead to the appearance of abdominal symptoms in this complication. In our case, the patient was completely asymptomatic, the radiographic pattern of cholangitis indicated a type of intrahepatic sclerosing cholangitis, and no other stenosis was observed in the ampulla of Vater.

The previously established diagnostic tools for HIV-associated cholangiopathy include US, CT, and ERCP. Although ERCP is considered to be the gold standard for the diagnosis and type classification of this disease (9), it is an invasive technique. MRCP is now increasingly being used as a non-invasive alternative imaging method, with high diagnostic accuracy for biliary involvement (10). In our case, MRCP could non-invasively detect biliary involvement, although no abnormalities were detected on abdominal US or contrast-enhanced CT.

Antimicrobial therapy against cytomegalovirus, protozoa, and bacteria in HIV-associated cholangiopathy is ineffective. Therefore, cART, which could radically enhance the immune reconstitution of patients, may be the best choice (11-13). Although several reports have shown that the initiation of cART in patients with HIV-associated cholangiopathy can improve the clinical symptoms and radiological findings (14, 15), little information is available regarding the effect of treatment on intrahepatic biliary duct stenosis because the modalities of ERCP and/or MRCP are required to observe the changes in the intrahepatic biliary duct. In our case, we demonstrated that intrahepatic biliary duct stenosis progressed even after the initiation of cART and normalization of the hepatic and biliary enzyme levels. Considering the possibility of cholangiocarcinoma development in HIV-associated cholangiopathy (16, 17), it is important to accurately identify and observe such patients using MRCP.

In conclusion, clinicians should keep in mind the possibility of HIV-associated cholangiopathy even in the era after the establishment of cART. A careful follow-up and detailed observation of biliary duct stenosis, as well as monitoring for neoplastic changes, are important even when the labora-

tory parameters indicating liver dysfunction show complete recovery after the initiation of cART.

The authors state that they have no Conflict of Interest (COI).

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