CASE REPORT

An unusual cause of oesophageal variceal bleeding in a Chinese human immunodeficiency virus–infected patient

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Non-cirrhotic portal hypertension is an unusual but potentially serious liver disorder in human immunodeficiency virus–infected patients with prolonged exposure to didanosine. Due to its rarity, the diagnosis is often delayed. It is postulated that didanosine contributes to obliterative portal venopathy and causes portal hypertension. Affected patients may present with abnormal liver function or signs of portal hypertension, while the diagnosis usually depends on liver biopsy. We report a case of non-cirrhotic portal hypertension in a human immunodeficiency virus–infected patient. The reported histological features include nodular regenerative hyperplasia and hepatoportal sclerosis. Early recognition is important as timely management of severe portal hypertension may prevent potentially fatal gastro-intestinal bleeding.

Introduction

We report a case of non-cirrhotic portal hypertension (NCPH) in a human immunodeficiency virus (HIV)–infected patient, related to prior exposure to the anti-retroviral medication, didanosine. To the best of our knowledge, this is the first confirmed case of this newly described clinical entity in Hong Kong.

Case report

A 45-year-old Chinese homosexual man was diagnosed to have acquired immunodeficiency syndrome in 1997 and started taking anti-retroviral medications in 1999. Initially he received lamivudine, stavudine, and nelfinavir. Due to drug-related diarrhoea and lipoatrophy, in 2002 his anti-retroviral regimen was changed to lamivudine, didanosine, and nevirapine. A year later, he was found to have a persistently high serum alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels, whose respective reference ranges were 163 to 352 IU/L and 168 to 650 IU/L. His serum alanine aminotransferase (ALT) and bilirubin levels were always within normal limits. He did not have a history of prior liver disease or excessive alcohol intake. Other investigations—including tests for hepatitis serology (hepatitis B surface antigen, anti–hepatitis C virus [HCV]), viral load assays (hepatitis B virus DNA and HCV RNA), autoimmune disease antibody screening (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, immunoglobulin levels), serum ceruloplasmin, iron saturation, and ferritin level—were all negative. The echocardiogram did not indicate a cardiac cause of liver cirrhosis. Transabdominal ultrasonography (USG) showed a mildly enlarged liver with a coarse echotexture, patent hepatic and portal veins, and mild splenomegaly measuring 13.0 cm in length. In 2006, didanosine was withdrawn after the patient developed drug-related acute pancreatitis. Since then, his HIV infection remained well controlled on treatment with lamivudine, abacavir, and nevirapine.

In February 2011, the patient had a haematemesis. Upper gastro-intestinal endoscopy confirmed the presence of grade III gastro-oesophageal varices with stigmata of recent haemorrhage. The variceal bleeding was controlled with repeated endoscopic band ligations. The patient's ALP and GGT levels remained persistently elevated 5 years after the discontinuation of didanosine. The spleen had enlarged to 16.0 cm when reassessed by USG. The HIV RNA level was still undetectable (<50 copies/mL) and the CD4 count remained low (85/mm^3) presumably as a consequence of hypersplenism. Transient elastography measured by FibroScan (Echosens, Paris, France) confirmed the presence of a stiff liver of 12.0 kPa. In view of the cryptogenic nature of portal hypertension, liver biopsy was eventually performed. Surprisingly, the characteristic dense fibrotic septa and nodules in liver cirrhosis were not found. Multiple densely fibrotic portal areas with small or absent portal venous branches (Fig 1) were identified. There were also herniations of portal vein

Key words
Anti-HIV agents; Didanosine; HIV infections; Hypertension, portal; Liver diseases

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一名HIV感染者的食道靜脈曲張破裂出血的罕見病因

非硬化性肝門靜脈高壓症很罕見，對於長期服食去羥肌苷（didanosine）藥物的HIV感染者來說更有機會引致嚴重肝病。此症罕見的特性往往會造成遲診。去羥肌苷可能導致肝門靜脈閉塞而引發肝門靜脈高壓症。患者會出現肝功能異常或肝門靜脈高壓症的症狀，而診斷通常依賴肝活檢。本文報告一名HIV感染者出現食道靜脈曲張破裂出血。其組織學特徵包括肝結節狀再生性增生及肝門靜脈硬化。盡快替病人確診可避免因嚴重肝門靜脈高壓而引致致命的胃腸道出血。

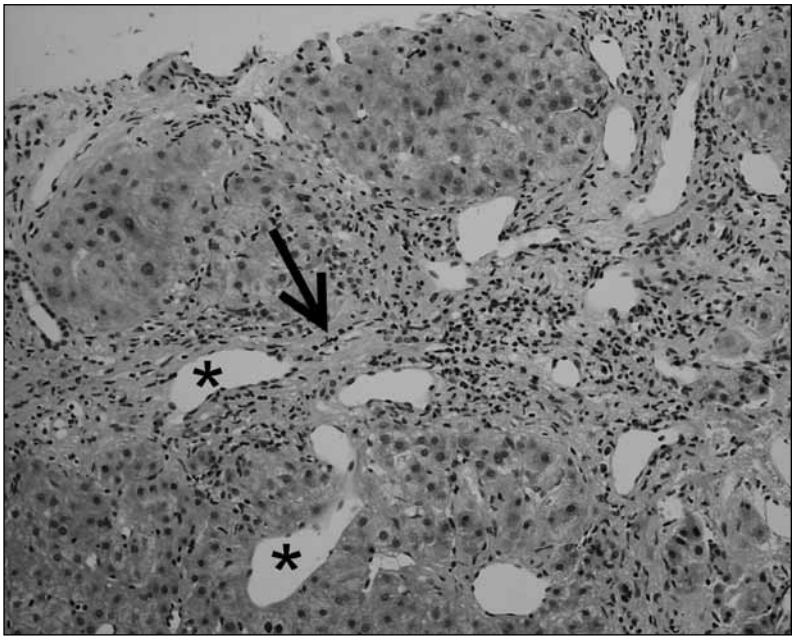

FIG 1. A densely fibrotic portal tract is shown with small or absent portal vein branches (arrow). Note the presence of markedly dilated sinusoids (*) [H&E, x 400]

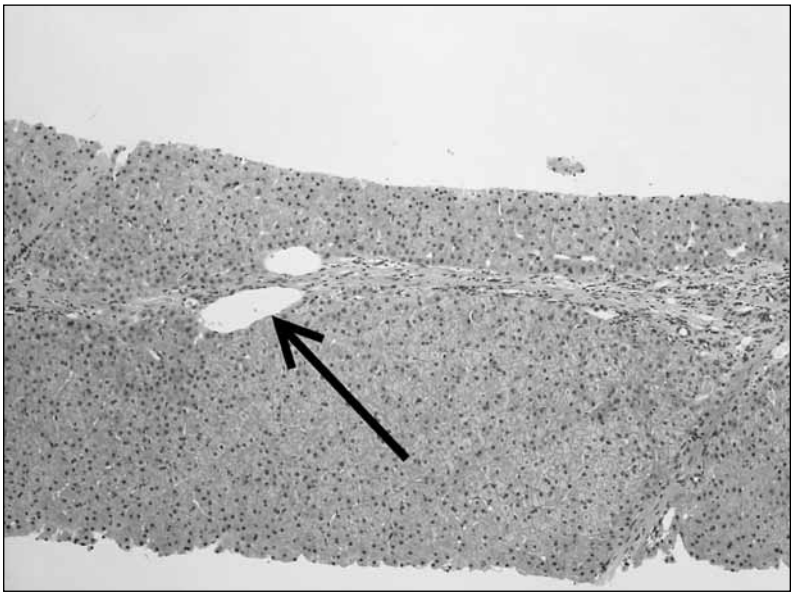

FIG 2. Herniation of portal vein branches into adjacent liver parenchyma (arrow) [H&E, x 400]

branches into the adjacent liver parenchyma (Fig 2). Features of nodular regenerative hyperplasia (NRH), viral inclusion bodies, or hepatic granuloma were not present. The constellation of clinical and histological findings was consistent with didanosine-induced liver injury leading to the development of hepatoportal sclerosis (HPS) and NCPH.

Discussion

In this era of anti-retroviral therapy, liver-related morbidity and mortality have become a major problem in HIV-infected patients.[1] Recently, an unusual but potentially fatal liver disorder known as NCPH has been described in a subset of patients with prolonged exposure to anti-retroviral therapy, particularly didanosine.[2,3] In view of emerging evidence, the US Food and Drug Administration issued a safety alert in January 2010 regarding the association of this potentially life-threatening complication in association with didanosine use.[4]

The clinical entity of NCPH is characterised by an increase in portal pressure due to prehepatic or intrahepatic causes in the absence of liver cirrhosis. Due to the lack of clinical awareness and rarity of the condition, the diagnosis is often delayed, as illustrated in our case. Moreover, it can easily be misdiagnosed as cirrhosis, especially if the patient has concomitant hepatitis B or C infections. Although the exact aetiopathogenesis remains poorly understood, evidence from case-control studies shows that NCPH should no longer be considered idiopathic.[5] In fact, it was reported to occur in association with a variety of autoimmune diseases, haematological disorders, and following medication with drugs such as azathioprine or 6-thioguanine.[6-9] Didanosine, the medication implicated in our case, was postulated to contribute by producing portal vascular endothelial damage through unknown mechanism in those who were genetically predisposed to develop obliterative portal venopathy and thus portal hypertension.[10]

Although didanosine-related NCPH has been widely described in the European cohorts,[5,11] to our knowledge, it has never been specifically reported in ethnic Chinese patients. The exact mechanism of hepatotoxicity remains poorly understood and no human leukocyte antigen–related genetic predisposition has been found. Clinically, patients are often asymptomatic and first present with signs of portal hypertension (ascites, hepatosplenomegaly, and oesophageal variceal bleeding), or more commonly with abnormal liver function tests.[12] A longstanding history of HIV infection and prolonged prior exposure to didanosine are universally recognised as causative.[10] The typical laboratory findings include moderate increases in serum ALP level and mild elevations of ALT. The majority of patients have preserved liver function

with normal albumin, bilirubin, and prothrombin levels.[10] Splenomegaly is the commonest findings on transabdominal USG. Portal vein thrombosis and cavernous transformation occur quite commonly in the setting of prolonged portal hypertension. Upper gastro-intestinal endoscopy reveals oesophageal varices in most cases. In our patient, the diagnosis of portal hepatopathy was unmasked only after the presentation with variceal bleeding. Another important implication of our report was the unremitting nature of hepatic vascular injury. This was shown by the fact that despite discontinuation of didanosine for 5 years, the portal hypertension continued to progress and subsequently lead to oesophageal variceal bleeding.

In view of the potentially serious complications of NCPH, this condition should always be considered in didanosine-exposed patients with persistently unexplained elevation of ALP levels. Liver biopsy is necessary to establish the diagnosis, particularly in the early stage of the disease. The reported histological findings of didanosine-related NCPH include NRH and less commonly, HPS[10] which was present in our patient's biopsy specimen. Advanced liver fibrosis is not typical with NCPH. The features of NRH and HPS may appear inconspicuous in a routinely processed needle biopsy and the findings may easily be overlooked if the diagnosis has not been considered.

As there is no specific therapy for didanosine-related NCPH, the treatment and prophylaxis of variceal bleeding have become the mainstay of management. Treatment with endoscopic band ligation and non-selective β-blockers may be effective in preventing acute bleeding. Transjugular intrahepatic portosystemic shunts may be an alternative for patients with variceal bleeding refractory to medical and endoscopic treatment. Although liver transplantation has been proposed for the management of NCPH,[13] it should only be reserved for patients with treatment-refractory complications or progressive liver failure.

Being a newly described condition in HIV-infected patients, NCPH has the potential to result in fatal upper gastro-intestinal bleeding. Physicians should be aware of the diagnosis in didanosine-exposed patients who have unexplained persistent elevation of ALP, splenomegaly, or oesophageal varices. Early recognition of the disorder and avoidance of the hepatotoxic medication are crucial in preventing irreversible liver damage.

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