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Case Report

Nodular regenerative hyperplasia of the liver combined with human immune-deficiency virus infection: a case report

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Abstract: Nodular regenerative hyperplasia (NRH) is associated with human immunodeficiency virus (HIV) infection. NRH may lead to non-cirrhotic portal hypertension (NCPH). The mechanism of NRH and NCPH in HIV-infected persons is still enigmatic. Here we present a case of NRH in a 43-year-old HIV-infected woman who had received highly active anti-retroviral therapy (HAART) for ten years. Afterwards, portal hypertension was determined by computed tomography in the patient and signs of suspected liver cirrhosis were detected by abdominal ultrasonography. Otherwise, no evidence of underlying liver diseases was found by following extensive examination. Ultimately NRH was indicated by liver biopsy. Non-selective β-adrenoceptor antagonist was administered to prevent esophageal variceal bleeding. In this case HAART was considered as the possible cause of NRH after other causes were excluded. Hence the risk of NRH should be noticed especially in patients with prolonged exposure to HAART.

Keywords: Nodular regenerative hyperplasia (NRH), highly active antiretroviral therapy (HAART), stavudine, tenofovir

Introduction

Nodular regenerative hyperplasia (NRH) is a rare condition, characterized by diffuse transformation of the hepatic parenchyma into regenerative nodules in the absence of fibrosis. The lesion does not conform to the definition of cirrhosis, which it sometimes resembles, with an incidence in autopsy studies of 2.6% [1-3]. NRH may be an important cause of non-cirrhotic portal hypertension (NCPH). Therefore, NRH and NCPH should be distinguished from liver cirrhosis. The first case of NRH was reported in association with Felty's syndrome in 1953 [4]. The phrase of "nodular regenerative hyperplasia" was coined by Paul E. Steiner in 1959 [5]. The most frequently associated pathological conditions are autoimmune disease, hematological malignancy, and HIV infection [6]. It has been reported that cumulative exposure to stavudine may lead to NRH [7], and tenofovir has also been related to NRH [6]. We herein report a rare case of NRH identified by a liver biopsy in an HIV-infected patient after receiving HAART including stavudine and tenofovir for 10 years.

Case report

A 43-year-old woman was hospitalized for 6 days beginning on May 26, 2015 due to worsening ventosity. Blood transfusion was undertaken in the case of postpartum hemorrhage after abortion in 1996. Neither addiction to alcohol or cigarette, nor family history of liver diseases was reported. After HIV infection was detected in 2004, nevirapine (200 mg bid), stavudine (40 mg bid), and lamivudine (150 mg bid) were administered in July 2005. The HAART was switched to lopinavir (200 mg bid), ritonavir (100 mg bid), tenofovir (300 mg qd), and lamivudine (150 mg bid) in June 2011. In total, the three main drugs of HAART, lamivudine, stavudine, and tenofovir were used for 517 weeks, 312 weeks, and 208 weeks respectively. Intermittent ventosity had been complained since early January 2011. Signs of liver cirrhosis, splenomegaly, and mild ascites were reported by ultrasound of the abdomen at a local primary medical care center in June 2013. On admission, vital signs of body temperature 36.7°C, pulse rate 80/min, respiratory rate 16/min, and blood pressure 130/80 mmHg were

Table 1. Laboratory test results on admission

Peripheral Blood		Hepatitis Virus	
WBC	2.55×10^9/L	Anti-HAV antibody	Negative
RBC	2.2×10^{12}/L	HBe antigen	Negative
HGB	56.3 g/L	HBs antibody	Positive
MCV	85.6 fl	Anti-HCV core antigen	Negative
MCH	25.44 pg	HCVRNA	Negative
PLT	41×10^9/L	Anti-HEV antibody	Negative
Blood Chemistry		Immunological Investigation	
Albumin	41 g/L	Anti-nuclear antibody	Negative
AST	16 U/L	Anti-smooth muscle antibody	Negative
ALT	12 U/L	Anti-mitochondrial antibody	Negative
ALP	52 U/L	Anti-dsDNA antibody	Negative
γ-GTP	18 U/L	Anti-cardiolipin antibodies	Negative
CREA	59 umol/L	ESR	15 cm/h

documented. Pale appearance was obvious in this patient. Splenomegaly was evidenced with spleen of medium harshness and palpable 5 cm below the costal margin. Hemorrhoids, liver-palms, spider-burst and hepatic encephalopathy were not detected. Blood routine test results were as follows, white blood cell (WBC) 2.55×10^9/L, red blood cell (RBC) 2.2×10^{12}/L, hemoglobin (HGB) 56.3 g/L, mean corpuscular volume (MCV) 85.6 fl, mean corpuscular hemoglobin (MCH) 25.44 pg, platelet (PLT) 41×10^9/L. Furthermore, neither abnormal result was found by the hepatic chemistry test [albumin 41 g/l, aspartate aminotransferase (AST): 16 U/L, alanine aminotransferase (ALT): 12 U/L, alkaline phosphatase (ALP): 52 U/L and γ-GTP: 18 U/L], nor the immunological markers of viral hepatitis, including anti-HAV, HBsAg, HBeAg, anti-HCV core antigen, HCV-RNA and anti-HEV. The serum creatine (59 umol/L) was normal. Neither markers of autoimmune-rated liver diseases including anti-nuclear, anti-smooth muscle, anti-mitochondrial, anti-dsDNA and anti-cardiolipin antibodies, nor personal or family history of autoimmune-related diseases could be determined. The erythrocyte sedimentation rate (ESR) was normal (15 cm/h) (**Table 1**).

Coarse echo waves of the liver parenchyma and nodules abnormally distributed across the liver were detected by abdominal ultrasonography. The maximum diameter of the spleen was measured as 18.1 cm and the caliber of spleen vein was 0.9 cm, implying obvious splenomegaly. Inhomogeneous density and nodular changes of the liver parenchyma were shown by abdominal computed tomography scanning (**Figure 1**), as esophageal varices without red color sign by esophagogastroduodenoscopy. Liver biopsy specimens were prepared, sectioned, and stained with hematoxylin-eosin (H&E) and masson protocols, demonstrating that the integrity of hepatic lobules was intact and regenerative nodular regions were abnormally distributed in the liver parenchyma, surrounded with atrophic hepatic plates and without any significant signs of fibrosis (**Figure 2**). NRH is characteristic of diffuse nodular hyperplasia in the liver parenchyma without accumulation of fiber, which was closely consistent with the histological features of this patient. Thus NRH was considered as the probable pathogenetic factor of related syndromes of this case and a non-selective β-adrenoceptor antagonist, propranolol (20-200 mg per day) was recommended to the patient to prevent development fatal combinations of portal hypertension, such as esophageal variceal bleeding. After the identification of NRH, the patient was discharged from hospital. The condition of the patient is being monitored currently and neither fatality nor severe complications have been reported.

Discussion

The pathogenesis of NRH remains unclear. Protein C and protein S deficiencies may be associated with the pathogenesis of NRH and the development of portal vein thrombosis in these patients. It has been shown that NRH may result from adaptive parenchymal changes due to irregular distribution of the blood supply, which is partly reversible. Histological alteration is based on local hepatocyte ischemia and compensatory hyperplastic lesions resulting from endothelial damage, obliterative portal venopathy, and sinusoidal injury. The unaffected adjacent hepatocytes form nodular hyperplasia [8]. In NRH, the hepatocyte hyperplasia or regeneration in the absence of fibrous tissue proliferation results in a nodular liver [5, 7]. The

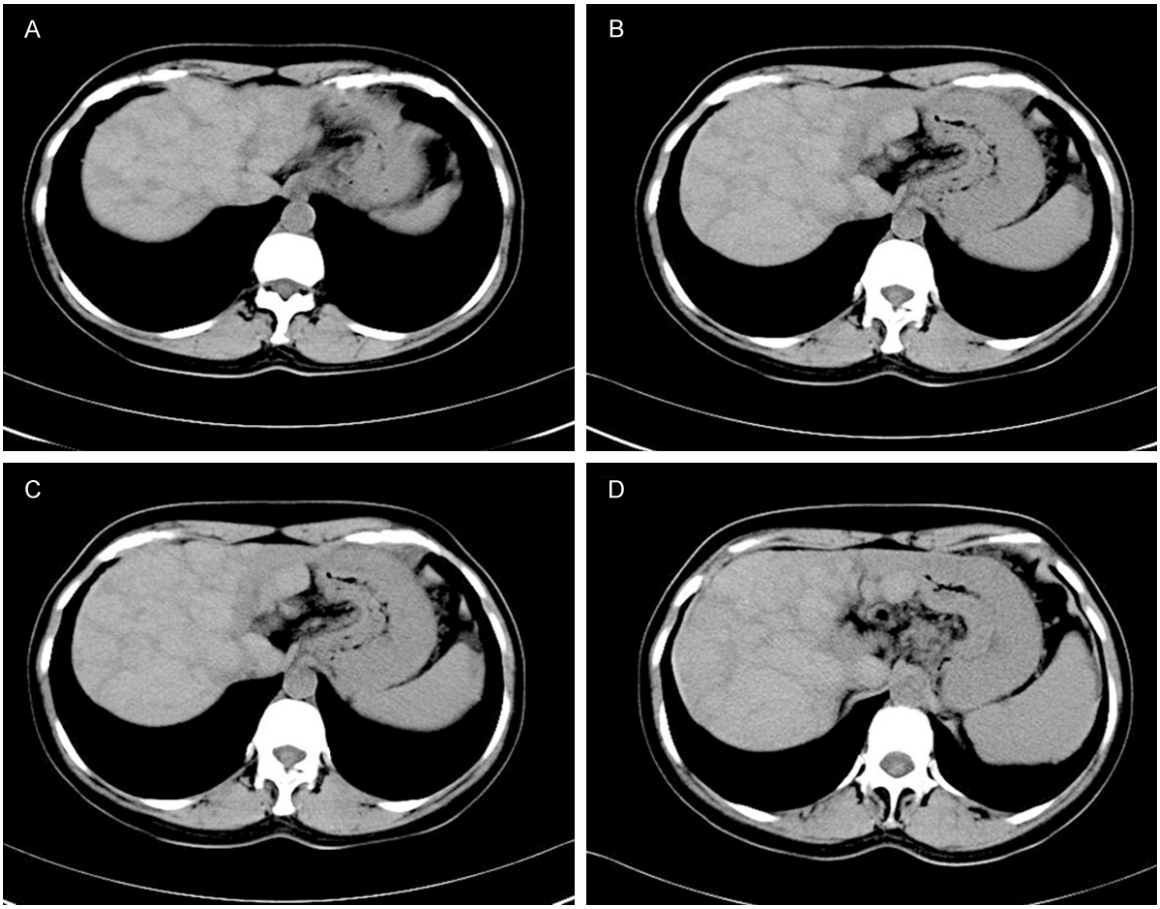

Figure 1. Abdominal CT imaging of the liver. A rough inner structure, central swelling and peripheral atrophy are revealed. Multiple nodules in the liver are apparently demonstrated. In addition splenomegaly is shown.

manifestations of portal hypertension, splenomegaly, were presented in this patient, which was followed by other signs of portal hypertension such as mild ascites and esophageal varices. Furthermore, diffuse regenerative nodular areas without surrounding by fibrous tissue in the liver parenchyma were shown by histological examination. Therefore, the diagnosis of the case as NRH could be considered as reliable. The diminution of the hemoglobin, white blood cell, and platelet counts might be attributed to splenomegaly. Additionally, patients with signs of portal hypertension should be differentiated with idiopathic portal hypertension (IPH). The histological characteristics of IPH are as follows: fibrous tissue proliferation seen in portal tracts, thickening of the intrahepatic portal branches wall, morphological abnomality of portal branches distribute in portal tracts, and some even connected to sinusoidal in hepatic lobule. Although this patient was observed with manifestations of portal hypertension and disturbed architecture with a nodular appearance in the liver parenchyma, characteristic of regenerative nodular areas of hyperplasia did not conform to the histological features of IPH. IPH typically features fibrous tissue proliferation in portal tracts. Thus IPH could be excluded for the diagnosis of the case. Considering NRH is a rare condition, which shares the portal hypertension signs with liver cirrhosis and hence is frequently misdiagnosed with cirrhosis, live biopsy is the vital protocol for further identification of the intriguing case.

Stavudine and tenofovir are nucleos(t)ide analogues (NA), of which the mechanism causing NRH is hypothetical. NA injures the cell directly through incorporating instead of the natural nucleosides into the retroviral nascent DNA strand. Besides, NA may also be incorporated into the mitochondrial DNA (mtDNA) by the human mitochondrial polymerase γ, Depletion of mtDNA, in turn, may lead to impaired mito-

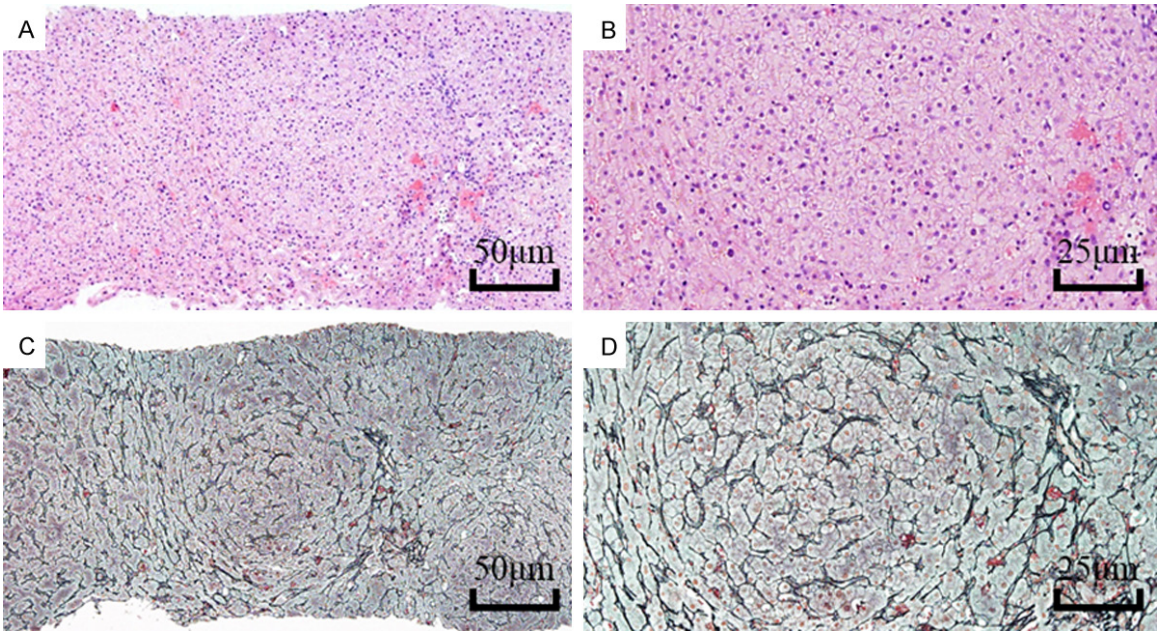

Figure 2. Histology of the liver biopsy specimen. (A, B) The integrity of hepatic lobules was intact. Regenerative nodular areas are abnormally distributed in the liver parenchyma, surrounded with atrophic hepatic plates and without any significant signs of fibrosis (H&E staining, original magnification A 100×, B 200×). (C, D) Multiple nodules in the parenchyma are shown, which are characteristic of nodular regenerative hyperplasia. Areas with thick hepatic plate adjacent to atrophic plate are also present. Atrophic hepatic cells are seen between the nodules, without any fibrosis (Masson, original magnification C 100×, D 200×).

chondrial function. This mitochondrial damage might injure hepatic endothelial cells [9]. The most commonly reported agents in drug-induced NRH including the thiopurines (azathioprine and thioguanine), oxaliplatin, stavudine, and didanosine [7]. In addition tenofovir may be related to NRH [6]. In this case the woman had accepted stavudine for 312 weeks and tenofovir for 208 weeks. Therefore we took into account the possibility that HAART might be responsible for the pathogenesis of NRH in this case.

The prognosis of NRH is influenced by the development of portal hypertension and its complications. Therefore, controlling portal hypertension provides the basis of therapeutic treatment for NRH [10]. At present the main treatment is removal of the offend agents, prevention and supportive care of manifestation, such as nonselective β-adrenoceptor antagonist, diuretics, endoscopic therapy, intrahepatic portal systemic shunt. Liver transplant is rarely attempted. The utility of anticoagulation in patients with NRH is a burgeoning concept [6]. However, it is important to note that there are cases in which NRH reappears in the transplanted liver [6, 11]. In the current paradigm, HAART is needed for HIV-infected patients in their entire life time, indicating that removal of the offending agents is infeasible and sometimes lethal for HIV-infected patients. In addition, the natural history of NRH is blurred and portal hypertension can progress despite discontinuation of offend agents. For the patient mentioned above, administration of propranolol rather than discontinuation of HAART was suggested as a rescuing approach. Although neither fatality nor severe complications had been reported since the discharge of the patient, further reexamination is needed to evaluate the progress of NRH in the patient.

The clinical manifestations of the cases found were highly variable. The most common presenting abnormality was abnormal hepatic function, existing in 51.8% of cases. Esophageal varices were detected in 81.3% of patients. In a series of the patients, gastrointestinal bleeding was observed in 62.5% of the cases. Ascites were found in 50.9% of the patients. Splenomegaly was detected in 46.4% of the patients. Other various clinical features of NRH were reported such as thrombocytopenia

Table 2. Presentations in patients with nodular regenerative hyperplasia and human immunodeficiency virus

Presentations	Cases n (%)	Source
Abnormal Hepatic Function	58 (51.8%)	Alvarez 2011; Bih 2010; Cachay 2011; Coelho 2015; Cotte 2011; Ding 2010; Fernandez 1993; Gulsen 2016; Hayano 2016; Hofmaenner 2011; Jin 2015; Lee 2017; Mallet 2007, 2009; Philips 2017; Sandrine 2007; Schiano 2011; Stebbing 2009; Tateo 2008; Vispo 2011
Thrombocytopenia	4 (3.6%)	Heimgartner 2016; Jin 2015; Lee 2017; Philips 2017
Abdominal Distention	2 (1.8%)	Arey 2007; Santiago 2012
Peripheral Edema	2 (1.8%)	Coelho 2015; Jin 2015
Splenomegaly	52 (46.4%)	Bihl 2010; Cesari 2010; Cotte 2011; Garvey 2007; Guo 2012; Heimgartner 2016; Lee 2017; Maida 2008; Mallet 2009; Podevin 2006; Sandrine 2007; Santiago 2012; Schiano 2011
Abdominal Pain	15 (13.4%)	Arey 2007; Bihl 2010 I; Gastroenterol; Cotte 2011
Epigastric Pain	2 (1.8%)	Fernandes 2016; Hofmaenner 2011
Ascites	57 (50.9%)	Alvarez 2011; Bihl 2010; Bissonnette 2012; Cesari 2010; Coelho 2015; Cotte 2011; Ding 2010; Dinh 2009; Fernandez 1993; in 2015; Mallet 2009; Podevin 2006; Saifee 2008; Sandrine 2007; Tateo 2008; Vispo 2011
Encephalophathy	6 (5.4%)	Dinh 2009; Lee 2017; Lopez 2014; Philips 2017
Esophageal Varices	91 (81.3%)	Alvarez 2011; Arey 2007; Bihl 2010; Bissonnette 2012; Cesari 2010; Cotte 2011; Ding 2010; Dinh 2009; Fernandez-Miranda 1993; Garvey 2007; Guo 2012; Heimgartner 2016; Kochin 2010; Kovari 2009; Lee 2017; Mallet 2007; Mallet 2009; Mendizabal 2009; Podevin 2006; Saifee 2008; Sandrine 2007; Schiano 2011; Schouten 2010; Tateo 2008; Vispo 2011
Gastrointestinal Bleeding	70 (62.5%)	Alvarez 2011; Bihl 2010; Bissonnette 2012; Cesari 2010; Cotte 2011; Ding 2010; Fernandez-Miranda 1993; Guo 2012; Heimgartner 2016; Kochin 2010; Lee 2017; Mallet 2007; Mendizabal 2009; Saifee 2008; Schouten 2011; Tateo 2008; Vispo 2011
Hepatocellular Carcinoma	1 (0.9%)	Lee 2017

References [6, 12-20].

(3.6%), abdominal distention (1.8%), abdominal pain (13.4%), epigastric pain (1.8%), encephalophathy (5.4%), hepatocellular carcinoma (0.9%) (**Table 2**). Severe portal hypertension with variceal bleedings and refractory ascites can precipitate cachexia and threaten life of these patients. Currently, the condition of the patient is stable. The clinical manifestations of this patient are splenomegaly, abdominal pain, and mild ascites. Neither fatality nor severe complications have been reported.

In summary, the possibility of NRH should be noticed in the HIV-infected patients undergoing long-term HAART. The presence of clinical portal hypertension in the patient with HIV-infection may be regarded as a clue of NRH and a liver biopsy is necessary.

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Disclosure of conflict of interest

None.

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