# Nodular Regenerative Hyperplasia in HIV-positive patients : a case series and review of the literature

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## Abstract

**Nodular regenerative hyperplasia (NRH) is a well-described condition that leads to non-cirrhotic portal hypertension and is histologically characterised by a nodular transformation of the liver without fibrosis. It seems to be a consequence of obliterative portal venopathy of small hepatic veins. Its precise aetiology remains to be clearly determined. NRH was reported to occur in HIV-positive patients ten years ago. In this article, three consecutive clinical cases of HIV-related NRH were identified in a high volume reference centre of HIV positive patients and are presented. Clinical, diagnostic aspects and strategies for management of this under-diagnosed medical condition in the HIV population are also developed.** (Acta gastroenterol. belg., **2017**, 80, **15-19**).

**Key words** : HIV, non-cirrhotic portal hypertension, Nodular Regenerative Hyperplasia.

## Introduction

The introduction of antiretroviral therapies at the end of the 1990s dramatically changed the management of HIV-positive patients and led to longer life expectancies (1,2). Since this major improvement, chronic liver diseases, together with cardiovascular and oncologic conditions, have become a major cause of mortality in this population (1,2).

Chronic liver diseases in HIV patients are mainly secondary to concomitant viral infection (co-infection with hepatitis B or C) and the progression of liver fibrosis is particularly increased in this scenario (2). Alcoholic and non-alcoholic steatohepatitis are also frequent in this population (2,3). However, when common causes of chronic liver disease in HIV-positive patients have been eliminated, some cases, including portal hypertension, still remain unexplained in this population (2). In this setting, a liver biopsy can be helpful for providing histological information and the diagnosis of nodular regenerative hyperplasia (NRH) can be done on histological samples (4). NRH should be systematically considered in the clinical context of unexplained portal hypertension in HIV patients (4).

NRH is a classical cause of non-cirrhotic portal hypertension (2). It is an acquired disease characterised by the presence of diffuse, small, and regenerative nodules that develop around portal spaces distributed evenly throughout the liver without significant fibrosis. Its prevalence in the general population has been estimated at between 0.72% and 2.6% based on two autopsy series from 1990 (5,6). NRH comprises 27% of all cases of non-cirrhotic portal hypertension in Europe (5,6,7).

The pathogenesis of NRH seems to be related to abnormalities of portal hepatic blood flow: local portal venous hypoperfusion leading to apoptosis and hepatocyte atrophy, and coexisting with local hyperperfusion and elevated levels of cell growth activators (5,8). The use of immunosuppressive medications or chemotherapeutic drugs is a classical cause of NRH due to damage caused to endothelial cells of small hepatic veins, but this condition may also develop via autoimmune, haematological, infectious, or neoplastic conditions (5). Ten years ago, NRH has been described in an HIV-positive cohort (8). The use of highly active antiretroviral therapy (HAART), including didanosine in particular, appears to play a major role in the pathophysiology of this disorder (5).

The present study reports our last ten-year experience in the management of HIV-related NRH. In this work, consecutive clinical cases of NRH in HIV patients are described.

## Methods

### *Study population*

Patients were identified in the clinical practices of the Infectious Disease and Hepatology departments of University Hospital Saint Pierre, Brussels. The records of the patients diagnosed with NRH were reviewed among all HIV-positive patients regularly followed at our outpatients clinic (approximately 2400 patients). Patients had to undergo a liver biopsy between January 2008 and December 2014 in the setting of non-cirrhotic portal hypertension.

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Submission date : 02/07/2016
Acceptance date : 31/08/2016

*Diagnosis of NRH*

The diagnosis of NRH was made by identifying diffuse nodules of hyperplastic hepatocytes with central, single portal tract and regions of internodular hepatocyte atrophy associated with areas of hepatocyte regeneration. The absence of extensive fibrosis was mandatory. Demographic data, details of symptoms, biochemical parameters, treatment, hospital course and follow-up were analysed. Follow-up data were obtained through regularly scheduled clinical visits. The specific aspects of NRH in the HIV population have been reviewed and a comprehensive review of literature on this topic was performed.

## Results

Three patients were identified during the study period. Cases are summarized in Table 1.

*Case 1*

A 68-year-old man was diagnosed as HIV-positive in 1994 when he was 46 years old. He had no medical history of alcoholism and no viral coinfection (hepatitis C virus [HCV] serology negative, hepatitis B surface antigen [HBSAg] negative). He received zidovudine (AZT) and didanosine treatment for 9 years, and then this treatment was discontinued. His treatment changed several times during the follow-up and was a combination of abacavir-lamivudine and darunavir-cobicistat at the time of presentation.

The patient had a history of arterial hypertension and benign prostate adenoma. He also had suffered repeated bouts of genital herpes since his HIV diagnosis, for which he received acyclovir. He started having abnormal liver function test results in 2002, while he was still on didanosine therapy. He was subsequently admitted for fatigue and blood tests disclosed pancytopenia: low serum haemoglobin level (8.5 g/dL), low platelet counts (71,000 per µL), and low leucocyte counts (1820 per mL). He also had slightly elevated aspartate aminotransferase levels (54 IU/L). At this time, his viral load was lower than 20 copies/mL and his CD4 count was 180/µL with a preserved CD4/CD45 ratio at 35%. The ultrasound revealed major splenomegaly and the diagnosis of hypersplenism was here assumed. The surface of the liver showed diffuse irregularity and hyperechoic hepatic nodules were described. Vascular axes (portal vein and hepatic veins) were permeable. Upper gastrointestinal (GI) endoscopy was performed and revealed the presence of large oesophageal varices. During a recent follow-up, a more detailed aetiological investigation for factors related to chronic liver disease (including auto-immunity, toxins, ceruloplasmin level, alfa-1 antitrypsin deficiency, and chronic hepatitis E) was negative. Transthoracic echocardiography was normal. Transjugular liver biopsy was performed: wedge hepatic venous pressure (WHVP) was 9 mmHg, free hepatic venous pressure (FHVP) was 3 mmHg, and the hepatic venous portal gradient (HVPG) was measured at 6 mmHg. Histological samples showed no or minimal perisinusoidal and portal fibrosis. Global liver histological architecture was preserved. A careful analysis of reticulin coloration confirmed a diffuse fine nodularity with centrally hypertrophied hepatocytes surrounded by atrophic hepatocytes. The final diagnosis was NRH.

The patient was treated with a non-selective beta-blocker and variceal band ligation as prophylaxis against GI haemorrhage. Anticoagulation was not proposed. After 1-year of follow-up, anaemia was resolved and no major clinical events were reported.

*Case 2*

A 46-year-old female patient tested positive for HIV in 1998, when she was 18, in the context of a pregnancy. Treatment with zidovudine was started. In 2001, treatment was changed to a combination of lamivudine-zidovudine, didanosine, and nevirapine.

One year later, upper GI endoscopy was performed in the context of suspected gastrooesophageal reflux and disclosed the presence of large oesophageal vari-

Table 1. — **Characteristics of the patients at the time of the first manifestation of portal hypertension**

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age | 54 | 44 | 33 |
| Sex | Male | Female | Male |
| HIV mode of contamination | Heterosexual | Heterosexual | Man who engages in sex with other men |
| Delay between HIV diagnosisand the first manifestation of NRH (years) | 8 | 14 | 6 |
| Didanosinetreatment (years) | 9 | 11 | 4 |
| CDC Class (4) | A | A | A |
| CD4 cell count at the time of the first manifestation (per µL) | 180 | 264 | 81 |
| Clinical manifestation | Pancytopenia | Asymptomatic oesophageal varices | GI hemorrhage |

CDC Class: Classification of the Centers for disease Control and Prevention

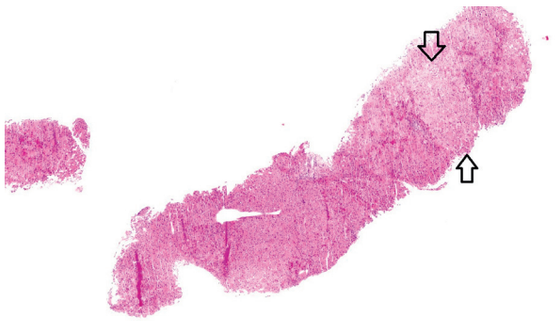

Fig. 1A — Liver biopsy on **hematoxylin** and eosin–stained sections: diffuse nodules of hyperplastic hepatocytes with central, single portal tract. Regions of internodular hepatocyte atrophy, centrilobular, associated with areas of hepatocyte regeneration.

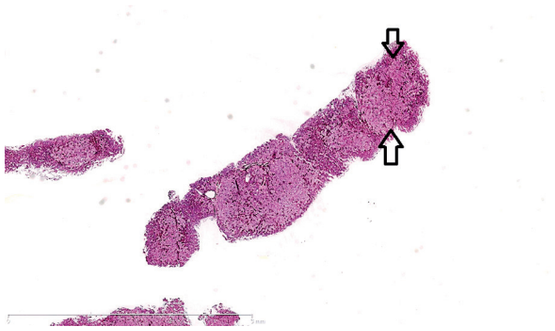

Fig. 1B — **Reticulin** stains highlights nodular architecture and hepatocyte atrophy.

ces. Blood tests were normal, with the exception of gamma glutamyltransferase, which was 6 times over the maximum normal limit. There was no anaemia, but her white blood cell level was 1840/mL and her platelet count was 87,000/µL. Viral load was undetectable, CD4 count was 264/µL with a CD4/CD45 ratio of 37%. This patient never suffered from alcohol abuse and had no HBSAg. HCV serology was negative. There were no known hepatotoxic medications and classical causes of chronic liver disease were excluded. Abdominal CT-scan revealed radiological signs of portal hypertension with splenomegaly and multiple oesophageal and gastric varices, in the absence of any liver abnormalities. Transjugular liver biopsy was performed, confirming the presence of portal hypertension (WHVP: 17 mmHg, FHVP: 5 mmHg, HVPG: 12 mmHg). Histological samples showed a pseudo-nodular aspect of the liver parenchyma confirmed by reticulin coloration (see Figure 1). A very discrete concomitant fibrosis was described. A diagnosis of NRH was established. The oesophageal varices were ligatured and non-selective beta-blockers were given. No anticoagulation was proposed. No major clinical events have been reported since then.

*Case 3*

A 52-year-old male patient was diagnosed with HIV infection at the age of 27, in 1991. Treatment with zidovudine was started. Two years later, didanosine was introduced and continued for 4 years. Treatment was subsequently changed to zidovudine, lamivudine, and indinavir. This combination treatment was maintained for 10 years. The patient was then moved to emtricitabine-tenofovir therapy, which remains his current treatment.

Six years after initiation of the anti-HIV treatment, the patient was admitted for massive GI haemorrhage. Upper-GI endoscopy disclosed large oesophageal varices and type 2 gastrooesophageal varices. After resolution of this haemorrhage, the patient remained pancytopenic (platelets: 45,000/µL, hemoglobin: 9.8 g/dL, white blood cells: 2200/mL). CD4 count was 81/µL with CD4/CD45 at 37%. Viral load was undetectable. Abdominal sonography confirmed large splenomegaly. There was no history of alcoholism, viral co-infection, or known hepatotoxic medication. The patient received non-selective beta-blockers and underwent regular follow-up.

In 2011, transjugular liver biopsy was performed and severe portal hypertension was found (WHVP: 37 mmHg, FHVP: 15 mmHg, HVPG: 22 mmHg). Histology did not reveal any fibrosis, but showed focal hypertrophy of hepatocyte spans associated with adjacent local atrophy. Reticulin staining confirmed a nodular shape and a final diagnosis of NRH was established. The patient suffered from repeated upper-GI haemorrhages. A transjugular intrahepatic portosystemic shunt (TIPS) was placed and HVPG was reduced to 13 mmHg.

Two years later, a new haemorrhage occurred secondary to a TIPS occlusion associated with a partial thrombosis of the superior mesenteric and splenic veins. This led to the insertion of a new TIPS with supplementary long lasting oral anticoagulation. Since then, no signs of GI bleeding recurrence have been noted.

## Discussion

NRH is a major cause of non-cirrhotic portal hypertension (9). It is due to the formation of small micronodules in liver parenchyma without concomitant fibrosis (2,8). Although the exact aetiology of NRH remains to be proven, there are different factors that contribute to its development. The most relevant one seems to be damage to the endothelium of small hepatic veins leading to an obliterative portal venopathy (OPV) (4,5). NRH is probably due to a compensatory hypertrophic response to impaired blood flow in the liver acini (5). This condition can appear during the course of systemic autoimmune disease or haemopathy such as myelodysplastic disorders, but also secondary to the use of several medications, including azathioprine, 6-mercaptopurine, or cyclophosphamide (Table 2). NRH and OPV have also been reported to occur with congenital or acquired prothrombotic states, including

Table 2. — **Main diseases and medications associated with NRH**

| | |
|---|---|
| **Treatments and medications** | Aziathioprine, Busulfan, Cytosine, Cyclophosphamide, Thioguanine, Carmustine, Chlorambucil, Doxyrubicin |
| **Diseases** | Rheumatoid arthritis/Felty's syndrome<br>Human immunodeficiency virus infection<br>Crohn's disease/ulcerative colitis<br>Celiac disease<br>Scleroderma/CREST, Lupus erythematosus<br>Lymphomas, myeloproliferative and Myelodysplastic syndromes<br>Coagulation disorders<br>Antiphospholipid syndrome<br>Macroglobulinemia<br>Mixed cryoglobulinemia<br>Primary biliary cirrhosis<br>Familial pulmonary fibrosis<br>Polyarteritis nodosa |

protein S deficiency (10). Moreover, 10 years ago it was reported that HIV patients could also develop this form of non-cirrhotic portal hypertension (8) and this is the condition we explored here.

Liver disease associated with HIV is currently a major clinical problem in this population (2,4). Classical causes of liver disease such as viral hepatitis co-infection or alcoholism are common in this population, and it is now becoming clear that conditions involving non-cirrhotic portal hypertension (including NRH, hepatic peliosis, and hepatoportal sclerosis) also appear to occur more frequently in HIV-positive patients (4,11). NRH secondary to OPV is one of these conditions.

To explain the development of vascular lesions in HIV patients, it has been hypothesized that HIV could directly damage hepatic endothelium (12,13). However, drug-induced hepatotoxicity seems likely to be the major explanation. Exposure to HAART has been systematically described in HIV patients with NRH (4,8,9). In particular, prolonged exposure to didanosine has been proven to be an independent risk factor for the development of this disorder (14). A potential detrimental effect associated with mitochondrial toxicity has been suggested (8,9,11,15). Didanosine was administered for years in the 3 clinical cases presented here. A new theory has been recently proposed to explain, at least partially, the development of OPV in HIV patients. It has been hypothesized that a prothrombotic state could predispose small hepatic veins to obstruction resulting in a lobulated regenerative state in the liver (10,16). Indeed, a high prevalence of pre-existing hypercoagulability, mainly due to protein S deficiency, has been reported in HIV patients with idiopathic non-cirrhotic portal hypertension and NRH (10,11). In HIV-positive patients, protein S deficiency is reported in 20% of patients after 15 years of HIV infection (10). Mallet et al. recently published that protein S activity was significantly lower in patients with HIV-related NRH as compared with HIV patients without NRH (10) suggesting functional inactivation of circulating protein S. It must be recognised that this type of full investigation of the prothrombotic state, including protein S level and activity, has not been performed in the 3 cases described here. In this small series, one patient had a HVPG measured at 6 mm Hg and one patient had 12 mm Hg. Assuming the hypothetical pathogenesis of NRH based on the obliterative portal venopathy, the portal hypertension should be related to a presinusoidal obstruction. In this case, the HVPG should be lower than 6 mm Hg. In the clinical practice, this is not always observed. One has to keep in mind that the exact pathogenesis of NRH is still unknown. In some systemic illnesses (polyarteritis nodosa by exemple), the primary insult may be directed at the hepatic artery rather than the portal vein radicles. The formation of the multiple nodules in the parenchyma could also participate to the intrahepatic block. An intrahepatic and sinusoidal block can be detected in HNR and the absence of a high HVPG is not systematically observed (17).

The prolonged asymptomatic subclinical period that characterizes NRH makes it difficult to establish a diagnosis before a serious complication occurs oesophageal varices haemorrhage being the most frequent (5). A vigilant attitude is warranted and liver biopsy should be performed if any clinical, radiologic, or biologic signs of unexplained portal hypertension are noticed in HIV patients (2). The clinical presentation of NRH includes portal hypertension (splenomegaly, oesophageal varices (OV), ascites) with or without elevation of transaminases.

Imaging methods are of little use in this setting and have poor sensitivity and specificity. A heterogeneous hepatic parenchyma may be the only imaging abnormality. On ultrasound, regenerative nodules are usually not visible while on computed tomography (CT), these nodules remain isodense or hypodense in both arterial and portal venous phases (4). A histological diagnosis can be made after careful examination by an experienced pathologist (4). The presence of small (about 3 mm) regenerative nodules without perisinusoidal or portal fibrosis on reticulin staining classically defines the diagnosis. Dilated sinusoids and thrombosed portal vein radicles are occasionally present (4).

There are no specific treatments for NRH, but the elimination of the causative factor, if established, is recommended (4). The mainstay of management remains the prevention and treatment of complications of portal hypertension, i.e. variceal bleeding, the main source of mortality (2,4). Treatment of portal hypertension and prevention of GI haemorrhage remain the cornerstone of management. Additionally, emphasizing the role of didanosine, some series showed improvement of liver tests and symptoms only 12 months after didanosine discontinuation (18,19). The potential deleterious effect of didanosine on portal tension has been highlighted repeatedly in the last decade and the European AIDS Clinical Society has cautioned clinicians about this side effect (20). Additionally, authors have argued that long-term anticoagulation treatment is indicated when thrombophilia is highlighted. Moreover, anticoagulation therapy has been found to be beneficial in the early stages of NRH induced by HAART in HIV-infected patients (4,14,21). It may slow the disease's progression by counteracting the hypercoagulable state, but further studies are warranted (4). If conservative portal-hypertension treatments fail (non-selective beta-blockers, variceal ligature, gastric vein obliteration), portal decompression with a TIPS is the next proposed step. Likewise, even though NRH is not usually associated with hepatic dysfunction (7), some cases of post-TIPS encephalopathy or symptoms of refractory portal hypertension have been reported (22). Liver transplantation may be indicated and has been successfully described in 7 HIV patients with NRH (14,23). The need for continued anticoagulant therapy after transplantation remains to be established (4).

These 3 clinical cases report non-cirrhotic portal hypertension related to NRH in HIV patients. These patients were identified in the clinical practice of a high volume reference centre of HIV positive patients: this clinical entity remains rare but is now well defined. NRH is a still under-diagnosed cause of liver disease in HIV-positive patients. It results in severe portal hypertension, frequently complicated by serious clinical events, such as oesophageal variceal bleeding. Early diagnosis seems to be the key to preventing unfavourable outcomes. This diagnosis requires a high index of suspicion and a prompt liver biopsy as soon as any signs of idiopathic portal hypertension are noticed.

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