

Non-Cirrhotic Portal Hypertension in Human Immunodeficiency Virus-Infected Patients: A New Challenge in Antiretroviral Therapy Era

Hortensia Álvarez Díaz*, Ana Mariño Callejo and José Francisco García Rodríguez

Infectious Diseases Unit, Department of Internal Medicine, Hospital Arquitecto Marcide-Profesor Novoa Santos, Ferrol, A Coruña, Spain

Abstract: Non-cirrhotic portal hypertension (NCPH) has been recently reported as a liver disease in Human Immunodeficiency Virus (HIV)-infected patients under antiretroviral therapy (ART). Combination of non-exclusive mechanisms has been described: primary endothelial damage of terminal portal veins induced by HIV or immunologic disorders, mitochondrial toxicity by didanosine and prothrombotic state. It is characterized by heterogeneous liver histological findings, frequently identified as nodular regenerative hyperplasia and clinical manifestations of portal hypertension with well-preserved liver function. We describe herein two HIV-infected patients with clinical picture suggestive of NCPH. Besides the case reports, we briefly address questions to apply to patient care in clinical practice.

Keywords: HIV, portal hypertension, didanosine.

INTRODUCTION

Non-cirrhotic portal hypertension (NCPH) is an emerging clinical condition reported in Human Immunodeficiency Virus (HIV)-infected patients controlled with antiretroviral therapy (ART), consisting of intrahepatic portal hypertension, in the absence of cirrhosis and other known etiologies of liver disease.

A multifactorial mechanism has been proposed to explain the pathogenesis of NCPH.

Pre-hepatic portal venulopathy [1], through primary endothelial cell injury by HIV or didanosine [2] (other adenosine analog, like azathioprine [3], have been reported to induce similar lesion). This damage might lead to obliteration of the small portal veins, ischemia of the supplied acini and regenerative hyperplasia of the remainders, in order to maintain liver cell mass.

Prothrombotic state, by HIV as a direct cause or through anti protein S antibodies [4], leading to protein S deficiency, results in an obliteration of the small portal venules and liver regenerative hyperplasia.

Therefore, didanosine and protein S low levels might be revealed as cofactors in pathogenesis of NCPH.

Pathologic hallmark would be a continuum and heterogeneous spectrum: subtle features which may be missed, *nodular regenerative hyperplasia* (also described in the setting of immunologic, malignant, hematologic and gastrointestinal infectious disorders), hepatoportal sclerosis [5] with the absence of advanced hepatic fibrosis or microvesicular steatosis (which could reflect mitochondrial damage induced by nucleoside reverse transcriptase

inhibitors, like didanosine [6]). *Presinusoidal portal hypertension* appears as the hemodynamic profile of NCPH, showing normal or mildly elevated (<10 mmHg) hepatic venous pressure gradient [7].

Didanosine has been postulated as an independent predictor of developing NCPH [6, 8], through cumulative dosing or idiosyncratic mechanisms [9]. Taking in account the last consideration, polymorphisms at genes involved in the metabolism of didanosine might predispose to veno-occlusive liver disease. In addition, removal of didanosine has appeared to be associated with clinical and laboratory improvements.

It is noteworthy that in guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (DHHS, December 1, 2009) [10], potential association with NCPH has been reported as an adverse event.

On the other hand, *portal thrombosis* has been frequently described at follow-up of NCPH. A 'two hit' model has been proposed [9]: portal endothelial damage, associated with long-term exposure of didanosine and repeated episodes of pylephlebitis, through disruption of intestinal barrier by HIV infection and anal sex practices in men who have sex with men (MSM), leading to reduced portal flow with added prothrombotic state, which might lead to develop portal thrombosis.

Despite the development of portal hypertension, liver synthetic function tests (prothrombin time, albumin) may be relatively well preserved, while progressive cholestasis and elevated serum aminotransferases appear on evolution. Decompensated liver pictures (ascites, bleeding due to esophageal varices) are frequent at the onset of clinical NCPH, through portal hypertension. In addition, portal thrombosis could be both the cause and consequence of liver decompensation.

We have identified two patients at our Spanish centre who fulfil the criteria for NCPH and we would like to describe them.

*Address correspondence to this author at the Infectious Diseases Unit, Department of Internal Medicine, Hospital Arquitecto Marcide-Profesor Novoa Santos, Avenida da Residencia, s/n, 15405, Ferrol, A Coruña, Spain; E-mail: hoaldi@gmail.com

CASE REPORTS

Case 1

A 58 year-old Caucasian man, a teacher in a primary school, was admitted to the hospital in February 2000, for evaluation of an esophageal ulcer and genital warts. HIV infection was diagnosed and antiretroviral therapy (ART) with zidovudine, lamivudine and nelfinavir was started. In January 2003, ART was changed to didanosine, stavudine and efavirenz, due to virological failure. Cholestasis and elevated serum aminotransferases appeared in blood test and infection with hepatitis B and hepatitis C virus was ruled out. A liver biopsy was performed in January 2004 and histology was unremarkable. In March 2004, ART was changed again to atazanavir/ritonavir booster and tenofovir, due to lipoatrophy linked to stavudine. Didanosine was continued. In September 2004, tenofovir was switched to backbone of zidovudine/lamivudine, due to hypophosphatemia and proteinuria associated with tenofovir. In December 2004, abdominal computed tomographic scan showed ascites and portal hypertension. In February 2005, an upper endoscopy revealed grade 3-4 distal esophageal varices and beta-blockers for primary prophylaxis of variceal bleeding were prescribed. Iron deficiency anemia appeared at follow-up and transfusion of several packed red cells was required. In June 2008, zidovudine was changed to abacavir to reduce hematologic toxicity. In September 2009 (under ART with abacavir, lamivudine, atazanavir/ritonavir and didanosine), the patient was admitted to the hospital because of bleeding from esophageal varices and he had to be transferred to intensive care unit to receive mechanical ventilation, hemodynamic support, pharmacotherapy (terlipressin) and banding ligation of esophageal varices. One month later, the patient was readmitted to the hospital because of new bleeding from esophageal varices, requiring banding ligation again. He was transferred to another hospital, where a transjugular intrahepatic portal systemic shunt (TIPS) was placed to connect the portal to right suprahepatic vein. Left branch portal vein thrombosis, mild splenomegaly and chronic liver disease were demonstrated by abdominal Doppler ultrasound. At discharge from hospital, didanosine was removed and the remainder antiretroviral scheme was continued (abacavir, lamivudine and atazanavir/ritonavir). Two months later, CD4 cell count was 131/mcl (12%) and viral load was below 50 copies/ml. Nowadays, the patient has a satisfactory general condition and he has been considered for liver transplantation [11].

Case 2

A 41-year-old Caucasian woman was admitted to the hospital in July 1998, because of *Pneumocystis jirovecii* pneumonia, oral candidiasis and pulmonary tuberculosis. HIV infection was diagnosed and ART with didanosine, stavudine and nevirapine was started. Two years later, progressive cholestasis appeared in blood test and infection with hepatitis B and hepatitis C virus was ruled out. In June 2003, the patient was admitted to the hospital because of bleeding from grade 2-3 esophageal varices. Sclerosis and banding ligation were performed, but main portal vein stent placement was required to connect the portal vein to inferior vena cava. Abdominal Doppler ultrasound showed massive ascites, left branch portal and splenoportal vein nonocclusive

thrombosis, as well as chronic liver disease. Autoimmunity parameters disclosed slightly positive anti-smooth muscle and negative antinuclear, antimitochondrial and anti-liver kidney microsomal antibodies. She was evaluated for hypercoagulable state and was found to have low antithrombin III values at the time of hematemesis. Sixteen months later, low protein C and S values were found. A liver biopsy showed patchy sinusoidal dilatation and congestion, collapsed liver cell plates and nodular areas without extensive fibrosis, all of these findings being suggestive of nodular regenerative hyperplasia. In April 2005, ART was changed to abacavir/lamivudine and lopinavir/ritonavir booster (didanosine was removed), due to virological failure and according to resistance test. An abdominal ultrasound performed in March 2009 showed patent shunt. Eight months later, CD4 cell count was 1005/mcl (36 %), viral load was below 50 copies/ml, and the patient had a satisfactory general condition.

DISCUSSION

Both patients had had heterosexual relationships as mode of HIV infection (nevertheless, in most of previous case series, predominance of MSM has been reported [8]). No liver enzyme elevations were noted before initiating ART and progressive cholestasis appeared after it (ART scheme including didanosine). They did not relate alcohol or other illicit drugs consumption and hepatitis B and C virus serology was negative. An evaluation of autoimmune parameters in second case did not reveal remarkable results. At the onset they presented with life-threatening upper gastrointestinal bleeding, under didanosine exposition of 6 years in first case (ascites and grade 3-4 esophageal varices had been noted four years before) and 5 years in second one. TIPS was required in first case and portal stent in second one. Left branch portal vein thrombosis was reported in both cases. Hypercoagulable state was not evaluated in first case, but protein C and S low levels were found in second patient (two determinations more than one year apart). Despite this finding, anticoagulation was not initiated. Liver biopsy was unremarkable in first case and findings compatible with nodular regenerative hyperplasia were disclosed in second one. Didanosine was removed from ART schema in both patients.

Questions and remarks arise from clinical practice:

- Referring to data regarding prothrombotic abnormalities in HIV-infected patients [12]: Should patients with HIV and non-cirrhotic portal hypertension be evaluated for hypercoagulable state?
- Risks linked to anticoagulation in this setting (i.e., bleeding from esophageal varices), above all if portal thrombosis appears, should be assessed.
- Removing didanosine from ART scheme should be considered. In addition, clinicians should be aware of novel long-term toxicities attributable to ART.
- High index of suspicion of NCPH, close monitoring of patent portal vein and risk of variceal hemorrhage, must be warranted.
- Which is the role of noninvasive methods (i.e., transient elastography or Fibro-test) for identification and monitoring of patients with NCPH in future?

REFERENCES

- [1] Saifee S, Joelson D, Braude J, *et al.* Noncirrhotic portal hypertension in patients with Human Immunodeficiency Virus-1 Infection. *Clin Gastroenterol Hepatol* 2008; 6 (10): 1167-9.
- [2] Maida I, Vispo E, Sotgiu G, *et al.* Unexplained severe portal hypertension in HIV-infected patients: a new clinical entity? *J Int AIDS Soc* 2008, 11(Suppl 1): P138.
- [3] Ferlitsch A, Teml A, Reinisch W, *et al.* 6-thioguanine associated nodular regenerative hyperplasia in patients with inflammatory bowel disease may induce portal hypertension. *Am J Gastroenterol* 2007; 102: 2495-503.
- [4] Pol S. Cryptogenetic liver disease, steatosis, portal hypertension, transaminitis and antiretrovirals. *J Int AIDS Soc* 2008; 11(Suppl 1): O24.
- [5] Schiano TD, Kotler DP, Ferran E, *et al.* Hepatoportal sclerosis as a cause of noncirrhotic portal hypertension in patients with HIV. *Am J Gastroenterol* 2007; 102(11): 2536-40.
- [6] Maida I, Núñez M, Ríos MJ, *et al.* Severe liver disease associated with prolonged exposure to antiretroviral drugs. *J Acquir Immune Defic Syndr* 2006; 42(2): 177-82.
- [7] Chang PE, Garcia-Pagan JC. Idiopathic noncirrhotic portal hypertension in HIV-infected patients. *Clin Infect Dis* 2010; 50(1): 127-8.
- [8] Kovari H, Ledergerber B, Peter U, *et al.* Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis* 2009; 49: 626-35.
- [9] Maida I, Garcia-Gasco P, Sotgiu G, *et al.* Antiretroviral-associated portal hypertension: a new clinical condition? Prevalence, predictors and outcome. *Antiviral Ther* 2008; 13: 103-107.
- [10] Guidelines for the use of Antiretroviral Agents in HIV-1- infected adults and adolescents. United States Department of Health and Human Services (DHHS). Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) December 1, 2009.
- [11] Tateo M, Sebah M, Bralet MP, *et al.* A new indication for liver transplantation: nodular regenerative hyperplasia in human immunodeficiency virus-infected patients. *Liver Transpl* 2008; 14: 1194-8.
- [12] Álvarez H, Mariño A, Garcia-Rodríguez FJ. Thrombotic events in Human Immunodeficiency Virus- infected patients: revisiting an emerging issue. *Infect Dis Clin Pract* 2009; 17 (4): 264-5.

Received: November 5, 2010

Revised: March 15, 2011

Accepted: March 16, 2011

© Díaz *et al.*; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.