NODULAR REGENERATIVE HYPERPLASIA IN HIV INFECTION: A PUZZLING CASE OF PORTAL HYPERTENSION IN A PATIENT COINFECTED WITH HUMAN IMMUNODEFICIENCY AND HEPATITIS C VIRUSES

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The case of a human immunodeficiency virus (HIV) and hepatitis C virus (HCV)-coinfected patient with a past medical history of deep venous thrombosis is presented. A liver biopsy, performed for unexpected finding of portal hypertension, showed vascular lesions presenting as nodular regenerative hyperplasia. Vascular liver diseases seem to be emerging as a new cause of chronic liver disease in HIV-infected patients under combined antiretroviral therapy. The syndrome of HIV-associated liver vasculopathy is discussed.

Key words: nodular regenerative hyperplasia; portal hypertension; HIV infection.

Liver disease is frequent in human immunodeficiency virus (HIV) infected patients. The decline in the mortality specifically related to HIV has revealed a growing mortality related to liver disease, which is now one of the leading causes of death of HIV-infected patients treated with antiretroviral combinations[1].

Liver disease in HIV-infected patients are usually secondary to toxicity of treatments, metabolic syndrome and lipodystrophy, excessive alcohol consumption and co-infection by one or several hepatotropic viruses[2, 3]. In some cases, no conventional cause can be found to explain abnormalities of liver function tests or portal hypertension in a patient with a long history of HIV infection, undetectable viral load and adequate immune restoration[4]. The prevalence, natural history, and pathophysiology of this recently described syndrome are unknown at the present time, but a number of cases appear to be due to vascular disease of the liver[5-10].

The authors report a clinical case that illustrates the diagnostic difficulty of liver disease in HIV-infected patients and the importance of histological examination to conclude when several liver diseases are involved.

This 42-year-old man, co-infected by HIV and the hepatitis C virus (HCV), was referred for alcohol withdrawal. HIV infection was detected in 1985. The identified risk factor for HIV and HCV infections was intravenous drug use at the age of 20. Triple-agent antiretroviral therapy comprising Didanosine (DDI), Lamivudine (3TC), Atazanavir and Ritonavir was started one year before this hospitalisation with effective control of HIV replication and a CD4 count of 427/mm^3 (17% of total lymphocytes). The patient had no history of opportunistic infection. Hepatic fibrosis had never been evaluated and hepatitis C had never been treated. He drank 120g of pure alcohol per day for more than seven years and smoked 20 cigarettes per day for more than 20 years. Five years previously, he experienced an episode of deep vein thrombosis of the left lower limb treated by oral anticoagulants for six months.

The patient was in a good general condition and had no chronic liver disease apart from abnormal visibility of the epigastric veins. Palpation of the liver was normal.

Liver function tests showed hepatic cytolysis predominantly affecting ALAT (2.5 times the upper limit of normal), elevation of GGT (twice the upper limit of normal), alkaline phosphatase (1.5 times the upper limit of normal), with bilirubin of 16µmol per litre, serum albumin of 40g per litre, and INR equal to 1. The platelet count was normal. There were no signs of iron overload, abnormal copper metabolism, metabolic syndrome, auto-immunity and the hepatitis B virus (HBV) genome was not detectable in serum by polymerization chain reaction (PCR). Abdominal ultrasound was normal. Upper GI endoscopy revealed grade II oesophageal and portal hypertension gastropathy.

Liver biopsy (20 mm long, 8 portal spaces examined) showed a typical appearance of nodular regenerative hyperplasia associated with mild perisinusoidal fibrosis and minimal enlargement of the portal spaces (Metavir A1F1). Clotting studies demonstrated protein S deficiency (activity 40%, antigen 44%) with no other associated abnormality (no Leyden mutation of factor V and factor II, no anti-phospholipid antibody, no circulating anticoagulant, no antithrombin III deficiency, normal homocysteine). The diagnosis was that of nodular regenerative hyperplasia associated with HIV infection in a heavy drinker co-infected by HCV, possibly due to a prothrombotic state.

Nodular regenerative hyperplasia is the second leading cause of noncirrhotic portal hypertension in the world[11]. The diagnosis is often difficult because of a nonspecific clinical presentation and segmental and focal liver lesions often leading to false-negative histological reports. In the absence of significant fibrosis on liver biopsy in a patient with portal hypertension, signs compatible with nodular regenerative

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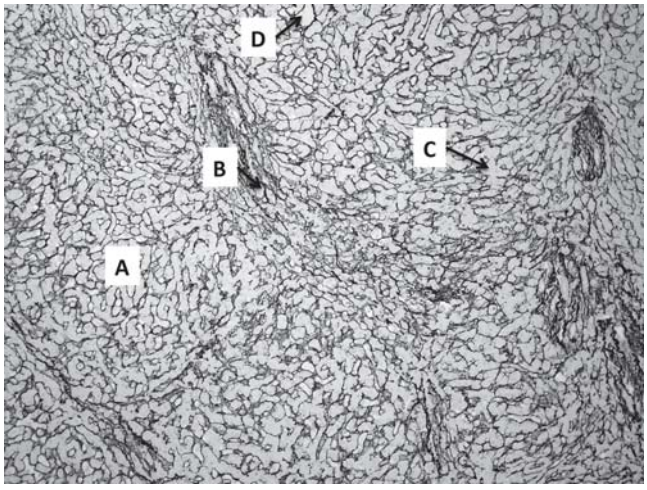
hyperplasia must be investigated: nodular architecture without fibrosis, association of thickened trabeculae and atrophic trabeculae, perisinusoidal fibrosis, sinusoidal dilatation (Figure 1)[12, 13].

Figure 1. Nodular regenerative hyperplasia: nodulation of the liver parenchyma with no significant fibrosis (A). Association of thickened (C) and compressed trabeculae (B) with areas of sinusoidal dilatation (D).



From a mechanistic point of view, nodular regenerative hyperplasia corresponds to a nonspecific adaptation of the hepatic parenchyma to a heterogeneous distribution of blood flow following occlusion of terminal branches of portal venules and/or hepatic arterioles[14, 15]. These hepatic vascular lesions are described in diseases predisposing to hepatic vascular occlusion either via thrombotic mechanisms (procoagulant states), endothelial lesions (drug toxicity), embolic mechanisms, especially septic (bartonelloses), modification of the hepatic blood flow (chronic hepatic congestion, arterial or venous thrombosis, hepatic lesions related to transplantation of a small-for-size graft)[16].

Nodular regenerative hyperplasia associated with HIV infection has been described only recently[7, 10]. The prevalence and mechanisms responsible for this syndrome are unknown. We are prospectively following a cohort of 23 HIV-infected patients referred to our department for chronic liver function test abnormalities and/or unexplained portal hypertension, who all present nodular regenerative hyperplasia. Three patients of our series underwent liver transplantation for severe liver failure and portal hypertension at the beginning of 2007. The three explanted livers were devoid of parenchymal fibrosis, and presented typical features of nodular regenerative hyperplasia and portal occlusive venopathy (Mallet V et al. AIDS 2009 in the press).

Nodular regenerative hyperplasia associated with HIV infection therefore appears to be due to occlusion of small portal venules, as previously described in the first reports by Ian Wanless[14, 15]. Clotting studies in all patients of this series revealed a selective deficiency of protein S (PS), a natural inhibitor of coagulation[17]. The prevalence of genetic PS deficiency in the general population is about 1/29.000. The probability of developing venous thrombosis with congenital PS deficiency increases with time: 50% at the age of 27 years and 70% at the age of 35 years[18]. Apart from congenital PS deficiency, acquired PS deficiency has also been described during pregnancy, oestrogen-progestagen contraception, systemic lupus erythematosus and nephrotic syndrome. PS deficiency has also been described in 15-20% of HIV-infected patients after more than 15 years of infection[19-21]. The pathophysiology of PS deficiency in HIV infection is unknown, but appears to be related to the duration of HIV infection and the presence of circulating auto-antibodies, possibly because of dysregulation of self-reactive antibody repertoires[22, 23].

In this clinical case, the presence of PS deficiency associated with a personal history of deep vein thrombosis was an argument in favour of a diagnosis of thrombophilia. As previously described, thrombophilia can be responsible for occlusive portal venopathy, secondary nodular regenerative hyperplasia and noncirrhotic portal hypertension. Thrombophilia is increasingly reported in association with HIV infection, especially in cohort studies, although the mechanism(s) has/have not been fully elucidated[21, 24]. It is possible that ageing of the population of HIV-infected patients could lead to the emergence of new diseases associated with HIV, including vascular diseases of the liver.

This clinical case illustrates the diagnostic difficulty of liver disease in HIV-infected patients in whom many causes of chronic liver disease may be involved. Nodular regenerative hyperplasia appears to be an emerging cause of chronic liver disease in HIV-infected patients revealed by the decline in mortality directly attributable to acquired immunodepression. The mechanisms responsible for these vascular diseases of the liver are only beginning to be elucidated.

References

1. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 34: 121-130, 2005.
2. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 42: 799-805, 2005.
3. Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J Hepatol 44: S132-S139, 2006.
4. Maida I, Nunez M, Rios MJ, et al. Severe Liver Disease Associated With Prolonged Exposure to Antiretroviral Drugs. J Acquir Immune Defic Syndr 42: 177-182, 2006.
5. Schiano TD, Kotler DP, Ferran E, Fiel MI. Hepatoportal Sclerosis as a Cause of Noncirrhotic Portal Hypertension in Patients With HIV. Am J Gastroenterol 102: 2536-2540, 2007.
6. Sandrine PF, Sylvie A, Andre E, et al. Nodular regenerative hyperplasia: a new serious antiretroviral drugs side effect? AIDS 21: 1498-1499, 2007.

7. Mallet V, Blanchard P, Verkarre V, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. AIDS 21: 187-192, 2007.
8. Garvey LJ, Thomson EC, Lloyd J, et al. Response to Mallet et al., 'Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients'. AIDS 21: 1494-1495, 2007.
9. Arey B, Markov M, Ravi J, et al. Nodular regenerative hyperplasia of liver as a consequence of ART. AIDS 21: 1066-1068, 2007.
10. Podevin P, Spiridon G, Terris B, et al. Nodular regenerative hyperplasia of the liver after IL-2 therapy in an HIV-infected patient. AIDS 20: 313-315, 2006.
11. Naber AH, Van Haelst U, Yap SH. Nodular regenerative hyperplasia of the liver: an important cause of portal hypertension in non-cirrhotic patients. J Hepatol 12: 94-99, 1991.
12. Steiner PE. Nodular regenerative hyperplasia of the liver. Am J Pathol 35: 943-953, 1959.
13. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 11: 787-797, 1990.
14. Wanless IR, Godwin TA, Allen F, Feder A. Nodular regenerative hyperplasia of the liver in hematologic disorders: a possible response to obliterative portal venopathy. A morphometric study of nine cases with an hypothesis on the pathogenesis. Medicine (Baltimore) 59: 367-379, 1980.
15. Wanless IR, Solt LC, Kortan P, et al. Nodular regenerative hyperplasia of the liver associated with macroglobulinemia. A clue to the pathogenesis. Am J Med 70: 1203-1209, 1981.
16. Reshamwala PA, Kleiner DE, Heller T. Nodular regenerative hyperplasia: not all nodules are created equal. Hepatology 44: 7-14, 2006.
17. Mallet VO, Viard JP, Lasne D, et al. Nodular regenerative hyperplasia in chronic human immunodeficiency virus infection is linked to protein S deficiency. J Hepatology 46: S274-S274, 2007.
18. Comp PC, Doray D, Patton D, Esmon CT. An abnormal plasma distribution of protein S occurs in functional protein S deficiency. Blood 67: 504-508, 1986.
19. Lafeuillade A, Alessi MC, Poizot-Martin I, et al. Protein S deficiency and HIV infection. N Engl J Med 324: 1220, 1991.
20. Sugerman RW, Church JA, Goldsmith JC, Ens GE. Acquired protein S deficiency in children infected with human immunodeficiency virus. Pediatr Infect Dis J 15: 106-111, 1996.
21. Levine AM, Vigen C, Gravink J, et al. Progressive prothrombotic state in women with advancing HIV disease. J Acquir Immune Defic Syndr 42: 572-577, 2006.
22. Stahl CP, Wideman CS, Spira TJ, et al. Protein S deficiency in men with long-term human immunodeficiency virus infection. Blood 81: 1801-1807, 1993.
23. Stahl D, Lacroix-Desmazes S, Misra N, et al. Alterations of self-reactive antibody repertoires in HIV disease: an insight into the role of T cells in the selection of autoreactive B cells. Immunol Lett 99: 198-208, 2005.
24. Klein SK, Slim EJ, de Kruif MD, Keller TT, ten Cate H, van Gorp EC, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. Neth J Med 63: 129-36, 2005.