A case of oesophageal varices and portal hypertension in an HIV-positive patient with no evidence of cirrhosis

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Abstract

We present a case of portal hypertension and variceal bleeding in the absence of cirrhosis, in an HIV-positive patient on long-term antiretroviral treatment with didanosine. We believe this to be the first such case identified in New Zealand (NZ).

Non-cirrhotic portal hypertension (NCPH) is a condition of elevated portal venous pressure in the absence of cirrhosis. NCPH was initially described in the Indian subcontinent in association with anaemia and congestive splenomegaly. It was initially referred to as ‘idiopathic portal hypertension’ or ‘hepatoportal sclerosis’.¹ A mechanism of thrombophlebitis as a result of recurrent gastrointestinal infection and repeated embolisation into the intrahepatic and extrahepatic portal venous circulation has been postulated to lead to increased portal venous pressure.²

In the developed world, NCPH is much less common. It has recently gained attention in the HIV-positive population following the publication of a number of reports linking antiretroviral exposure to the development of NCPH. It has not previously been described in NZ.

An estimated 1230 HIV-infected individuals were receiving medical care in NZ in 2007,³ 0.03% of the general population. Exposure to patients with complications of HIV and treatment is therefore low amongst non-specialist medical services.

Case report

A 49-year-old man was brought in by ambulance to this centre following sudden onset nausea and multiple bouts of vomiting of fresh blood. He had a 3-week history of intermittent abdominal pain prior to this event. He had no previous gastric symptoms or NSAID use and drank alcohol occasionally. He had no previous liver dysfunction or infection with hepatitis A, B or C.

He was diagnosed with HIV in 1996 at which time he was asymptomatic with a CD4 count of less than 200x10⁶/L. Antiretroviral therapy (ART) was commenced in early 1999. He had been treated initially with 3 years of stavudine 40 mg bd, abacavir 300 mg bd and nelfinavir 1250 mg bd. This was changed in 2002 to a regimen of didanosine 250 mg po od, efavirenz 600 mg od and tenofovir 300 mg od. His disease at time of this presentation was stable with an undetectable HIV viral load and a CD4 count of 290x10⁶/L. He was believed to be adherent to the antiretroviral regimen as detailed above.

On examination he was pale, thin and afebrile. He had mild epigastric tenderness, but no peritonism. There was no ascites or encephalopathy. Rectal examination revealed dark stools with no blood or melaena.
The haemoglobin on admission was 115 g/L which dropped to 90 g/L the following day. Further blood tests revealed—bilirubin 9 umol/L (2–22), ALP 71 g/L (40–110), ALT 26 U/L (0–45), GGT 135 U/L (0–60), INR 1.1, and albumin 36 g/L (38–52). Blood tests excluded the presence of hepatitis A, B, and C. Alpha-1-antitrypsin, iron studies, ANA and smooth muscle antibodies, serum immunoglobulins and ceruloplasmin were all normal.

At endoscopy, four large varices were noted protruding to half of the lumen with a platelet plug visible at an obvious recent bleeding site (Figure 1). A moderate amount of altered transported blood was found in the stomach. Six variceal bands were applied. Prominent fundal folds were noted raising the possibility of fundal varices. No obvious portal gastropathy was seen.

Figure 1. Endoscopic view of oesophagus with four large varices and a platelet plug indicating the site of recent haemorrhage

An ultrasound scan of the liver demonstrated slightly coarse echotexture but no focal hepatic parenchymal pathology was seen. There was no evidence of macronodular change and normal anterograde flow was seen in the portal and hepatic veins. Portal
venous flow was measured at 10 cm/second, which is within the normal range. The spleen was slightly prominent at 14 cm in length. No perisplenic varices were seen.

A Fibroscan showed a transient elasticity of 5.9 kPa (IQR 1.0 kPa, 10/10 recordings valid), consistent with minimal or no fibrosis. He declined to have a liver biopsy.

The patient’s ART was changed to tenofovir 300 mg od, efavirenz 600 mg od and abacavir 600 mg od, and propranolol 40 mg bd was commenced as secondary prophylaxis of variceal haemorrhage. Elective oesophageal banding was performed on a further three occasions during the subsequent 12 months with consequent reduction in varix size. He has not suffered any further episodes of bleeding.

**Discussion**

In patients who are HIV-positive, liver disease is usually due to concurrent chronic viral hepatitis, alcohol abuse or non-alcoholic steatohepatitis. NCPH is a relatively newly described condition in patients who are HIV-positive and has potentially life-threatening sequelae, particularly variceal haemorrhage. The pathogenesis of this condition is not well understood. In the HIV-positive population, an increased incidence of NCPH has been found in those exposed through anal intercourse.

It has been hypothesised that transfer of microbes from the gastrointestinal tract to the portal circulation and the resulting septic microthrombophlebitis could account for the development of NCPH in this group. In the Indian subcontinent, ‘necirrhotic portal fibrosis’ (NCPF) has been described, and accounts for approximately a quarter of all variceal bleeding seen within that region. Similarly, the most widely proposed mechanism in the development of NCPF is fibrosis due to recurrent microembolism in the portal circulation secondary to abdominal sepsis.

NCPH has been defined in a recent case-control study as the presence of endoscopically documented oesophageal varices or an hepatic venous pressure gradient >10 mmHg, no cirrhosis on liver biopsy, and the absence of alternative aetiologies (hepatitis B, C, alcohol excess, haemochromatosis, Wilson’s disease, alpha 1 antitrypsin deficiency, autoimmune hepatitis, non alcoholic fatty liver disease or hepatotoxic drugs).

Liver biopsy in patients with NCPH may reveal a variety of histologic lesions, though these are not consistently present. They include perportal fibrosis, perisinusoidal fibrosis, and nodular regenerative hyperplasia. These histological features are consistent with a pathophysiological mechanism of presinusoidal fibrosis leading to obstructive portal venopathy and intrahepatic portal hypertension. By definition liver cirrhosis is absent on biopsy, and the clinical sequelae of variceal haemorrhage and ascites are a consequence of portal hypertension. However liver failure leading to death or liver transplantation has been described in some cases of NCPH.

Prognosis for patients with antiretroviral associated NCPH has not been clearly described. In a published cohort 4/15 patients died of complications of liver disease, either variceal haemorrhage or liver failure, over an average follow-up period of 12 years. In addition NCPH is a rare but recognised cause of decompensated liver disease.
requiring liver transplantation. Ongoing monitoring of patients with antiretroviral associated NCPH for these complications is therefore warranted.

Although our patient declined liver biopsy, the Fibroscan result excluded hepatic fibrosis or cirrhosis. Fibroscan is a well-validated non-invasive method for detecting hepatic fibrosis or cirrhosis. A recent meta-analysis of 50 studies examining the performance of Fibroscan showed that cirrhosis could be excluded with a transient elasticity (TE) of less than 13.01 kPa, and significant hepatic fibrosis (equivalent to a metavir score of F2 or greater on liver biopsy) with a TE less than 7.65 kPa.

Didanosine has recently been implicated in the development of NCPH. Its use in NZ has declined due to well-documented toxicity issues such as lipodystrophy, pancreatitis and lactic acidosis. Exposure to any ART medication appears to increase the risk of developing NCPH, and this risk appears to be cumulative. ART commenced as mono or dual therapy increases the risk when compared to three or more drugs. When individual antiretrovirals were studied, didanosine stood out as a risk factor for development of NCPH, with an odds ratio of 3.44.

Our report describes an HIV-positive patient treated with didanosine for 8 years. He presented with variceal haemorrhage secondary to portal hypertension, had no evidence of liver fibrosis or cirrhosis on Fibroscan and had a negative screen for causes of chronic liver disease. This is the first report of didanosine associated NCPH identified in NZ.

The population of individuals infected with HIV in NZ remains small and current ART regimes are highly effective. Nevertheless, it is important that clinicians remain vigilant for unusual complications of the disease and its therapy.

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