An unusual cause of oesophageal variceal bleeding in a Chinese human immunodeficiency virus–infected patient

Non-cirrhotic portal hypertension is an unusual but potentially serious liver disorder in human immunodeficiency virus–infected patients with prolonged exposure to didanosine. Due to its rarity, the diagnosis is often delayed. It is postulated that didanosine contributes to oblitative portal venopathy and causes portal hypertension. Affected patients may present with abnormal liver function or signs of portal hypertension, while the diagnosis usually depends on liver biopsy. We report a case of non-cirrhotic portal hypertension in a human immunodeficiency virus–infected patient. The reported histological features include nodular regenerative hyperplasia and hepatoporal sclerosis. Early recognition is important as timely management of severe portal hypertension may prevent potentially fatal gastro-intestinal bleeding.
Discussion

In this era of anti-retroviral therapy, liver-related morbidity and mortality have become a major problem in HIV-infected patients. Recently, an unusual but potentially fatal liver disorder known as NCPH has been described in a subset of patients with prolonged exposure to anti-retroviral therapy, particularly didanosine.2,3 In view of emerging evidence, the US Food and Drug Administration issued a safety alert in January 2010 regarding the association of this potentially life-threatening complication in association with didanosine use.4

The clinical entity of NCPH is characterised by an increase in portal pressure due to prehepatic or intrahepatic causes in the absence of liver cirrhosis. Due to the lack of clinical awareness and rarity of the condition, the diagnosis is often delayed, as illustrated in our case. Moreover, it can easily be misdiagnosed as cirrhosis, especially if the patient has concomitant hepatitis B or C infections. Although the exact aetiology remains poorly understood, evidence from case-control studies shows that NCPH should no longer be considered idiopathic.5 In fact, it was reported to occur in association with a variety of autoimmune diseases, haematological disorders, and following medication with drugs such as azathioprine or 6-thioguanine.6-9 Didanosine, the medication implicated in our case, was postulated to contribute by producing portal vascular endothelial damage through unknown mechanism in those who were genetically predisposed to develop obliterative portal venopathy and thus portal hypertension.10

Although didanosine-related NCPH has been widely described in the European cohorts,5,11 to our knowledge, it has never been specifically reported in ethnic Chinese patients. The exact mechanism of hepatotoxicity remains poorly understood and no human leukocyte antigen-related genetic predisposition has been found. Clinically, patients are often asymptomatic and first present with signs of portal hypertension (ascites, hepatosplenomegaly, and oesophageal variceal bleeding), or more commonly with abnormal liver function tests.12 A longstanding history of HIV infection and prolonged prior exposure to didanosine are universally recognised as causative.10 The typical laboratory findings include moderate increases in serum ALP level and mild elevations of ALT. The majority of patients have preserved liver function...
with normal albumin, bilirubin, and prothrombin levels. Splenomegaly is the commonest findings on transabdominal USG. Portal vein thrombosis and cavernous transformation occur quite commonly in the setting of prolonged portal hypertension. Upper gastro-intestinal endoscopy reveals oesophageal varices in most cases. In our patient, the diagnosis of portal hepatopathy was unmasked only after the presentation with variceal bleeding. Another important implication of our report was the unremitting nature of hepatic vascular injury. This was shown by the fact that despite discontinuation of didanosine for 5 years, the portal hypertension continued to progress and subsequently lead to oesophageal variceal bleeding.

In view of the potentially serious complications of NCPH, this condition should always be considered in didanosine-exposed patients with persistently unexplained elevation of ALP levels. Liver biopsy is necessary to establish the diagnosis, particularly in the early stage of the disease. The reported histological findings of didanosine-related NCPH include NRH and less commonly, HPS which was present in our patient's biopsy specimen. Advanced liver fibrosis is not typical with NCPH. The features of NRH and HPS may appear inconspicuous in a routinely processed needle biopsy and the findings may easily be overlooked if the diagnosis has not been considered.

As there is no specific therapy for didanosine-related NCPH, the treatment and prophylaxis of variceal bleeding have become the mainstay of management. Treatment with endoscopic band ligation and non-selective β-blockers may be effective in preventing acute bleeding. Transjugular intrahepatic portosystemic shunts may be an alternative for patients with variceal bleeding refractory to medical and endoscopic treatment. Although liver transplantation has been proposed for the management of NCPH, it should only be reserved for patients with treatment-refractory complications or progressive liver failure.

Being a newly described condition in HIV-infected patients, NCPH has the potential to result in fatal upper gastro-intestinal bleeding. Physicians should be aware of the diagnosis in didanosine-exposed patients who have unexplained persistent elevation of ALP, splenomegaly, or oesophageal varices. Early recognition of the disorder and avoidance of the hepatotoxic medication are crucial in preventing irreversible liver damage.

References