CASE REPORTS

Steatohepatitis due to Antiretroviral Therapy

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ABSTRACT

Jamaica has recorded the largest increase in the rate of HIV/AIDS infection in the English-speaking Caribbean since 1985. Treatment has significantly improved recently with approximately 50% availability of antiretrovirals (ARVs) to patients. The incidence of drug induced hepatotoxicity is not well known for most ARV drugs and few studies have assessed adverse drug effects in clinical practice. A patient with HIV on highly active antiretroviral therapy (HAART) presented with a one year history of progressive abdominal distension. Abdominal examination revealed a 17 cm, smooth, non-tender liver with a rounded edge; 12 cm of which was below the right costal margin. Liver enzymes were grossly abnormal. The liver biopsy revealed parenchymal distortion by fibrosis with macrovesicular fatty change and Mallory's hyaline in keeping with steatohepatitis. Follow-up studies after discontinuation of stavudine revealed that the liver enzymes improved within four months. Physicians should be mindful of the hepatotoxic potential of ARVs and monitor liver enzymes in HIV-infected patients on therapy.

Esteatohepatitis Debido a la Terapia Antiretroviral

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RESUMEN

Jamaica ha registrado el mayor aumento de la tasa de infección de VIH/SIDA en el Caribe anglófono desde 1985. El tratamiento ha mejorado recientemente de manera significativa, con una disponibilidad de 50% de antiretrovirales (ARVs) para pacientes. La incidencia de la hepatotoxicidad inducida por medicamentos no es conocida para la mayoría de los medicamentos ARV y pocos estudios han evaluado los efectos adversos de esos medicamentos en la práctica clínica. Un paciente con VIH, sometido a una terapia antiretroviral altamente activa, se presentó con una historia de distensión abdominal progresiva de un año. El examen abdominal reveló un hígado de 17 cm, liso, no blando, y de bordes redondeados, 12 cm del cual se hallaban por debajo del margen del costado derecho. Las enzimas del hígado eran evidentemente anormales. La biopsia del hígado reveló una distorsión parenquimatosa por fibrosis con cambio graso macrovesicular y formación de hialina de Mallory en correspondencia con la esteatohepatitis. Los estudios de seguimiento tras la discontinuación de la estavudina, revelaron que las enzimas del hígado mejoraron en cuatro meses. Los médicos deben tomar conciencia del potencial hepatotóxico de los ARVs y monitorear las enzimas del hígado en pacientes infectados con el VIH que se hallen bajo terapia.

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INTRODUCTION

Since the diagnosis of the first patient with HIV in Jamaica in 1982, the incidence of HIV disease in Jamaica has increased from 0.5 per 100 000 in 1985 to 1.5 per 100 000 in 2001. In fact, Jamaica has recorded the largest increase in the rate of

HIV/AIDS infection of any English-speaking Caribbean country since 1985 (1).

As a region, the Caribbean is the second most affected by HIV/AIDS per capita with about 2.4% of the adult population living with this disease which has become one of the leading causes of death in persons 15–44 years old (1). It is also responsible for an estimated 80 000 Caribbean children being orphaned (1). With such a heavy patient burden, it was reported that between 2002 and 2003, less than 5% of those who needed therapy with antiretrovirals (ARVs) were actually receiving it. (2). This was largely a consequence of the prohibitive costs of these drugs. However, the care of these patients, in Jamaica, has been significantly boosted in 2004 through partnerships with the Global Fund. This has resulted in approximately 50% availability of antiretrovirals to patients (2).

With the widespread availability of highly active antiretroviral therapy (HAART) in the middle of the 1990s, there has been a decline in the prevalence of various AIDS-defining conditions with resultant decreased morbidity and mortality (3). However, improved survival has resulted in a new subset of patients emerging in whom clinical entities associated with longstanding HIV disease have developed. In addition, HAART therapy has the potential for several side effects including hepatic injury (4). The incidence of drug induced hepatotoxicity is not well known for most antiretroviral drugs and few studies have assessed the incidence of adverse drug effects in HIV infection in clinical practice (5). Although the nucleoside analogue reverse transcriptase inhibitors (NRTI) have been reported to cause fatty liver disease (6), there are no reports of hepatotoxicity with HAART previously reported from the Caribbean. A patient who developed steatohepatitis due to ARV therapy is hereby presented.

CASE REPORT

A 32-year old homosexual male was diagnosed with HIV disease in 1991. He presented to the outpatient department of the University Hospital of the West Indies, Jamaica, in July 2005 with a one year history of progressive abdominal distension which had worsened over the preceding three months. He had associated early satiety and anorexia and 30 lb weight loss. There was no nausea, vomiting, epigastric pain nor jaundice. He complained of passing brown watery stool without blood or mucous approximately 5–6 times daily for the last three months.

He had taken HAART therapy erratically for 18 months prior to 2004 mostly because of financial constraints. During this period, he was also non-compliant with follow-up and was often adjusting the doses of medications on his own. He did not use any over-the-counter drugs. He neither smoked, drank alcohol nor bush tea. In January 2004, he was started on a new regime of stavudine, lamivudine and efavirenz with which he was fully compliant.

On examination, his vitals signs were normal; waist: hip ratio of 1.25 with body mass index (BMI) of 23.5. He had loss of fat from his face, arms and thighs. Of note, no icterus, oral candidiasis or lymphadenopathy were detected. He had no peripheral stigmata of chronic liver disease. Examination of his respiratory, cardiovascular and neurological systems were unremarkable. Abdominal examination revealed a 17 cm, smooth, non-tender liver with a rounded edge; 12 cm of which was below the right costal margin. The spleen was not palpated. Clinically, there was no ascites. The abdominal ultrasound showed a grossly enlarged liver with increased echogenicity; no focal lesions were seen.

Laboratory tests done in 2002 and 2004 revealed normal complete blood count, liver function tests and electrolytes. In 2005, approximately one year after the new HAART regime, the alkaline phosphatase (626 iu/l), transminase (SGOT 386 iu/l) and GGT (1336 iu/l) were grossly elevated with normal bilirubin levels. Hepatitis B and C screens were negative. His $CD4^+$ T cell count was 150/uL with a viral load of 10 000 copies per millilitre. The liver biopsy revealed parenchymal distortion by fibrosis with macrovesicular fatty change and the presence of Mallory's hyaline in keeping with steatohepatitis (Figure). Stavudine and efavirenz were discontinued; tenofovir and kaletra (lopinavir/ritonavir) were added to lamivudine. Follow-up studies revealed that the liver enzymes improved significantly within four months with the transminases falling below three times upper limit of normal values.

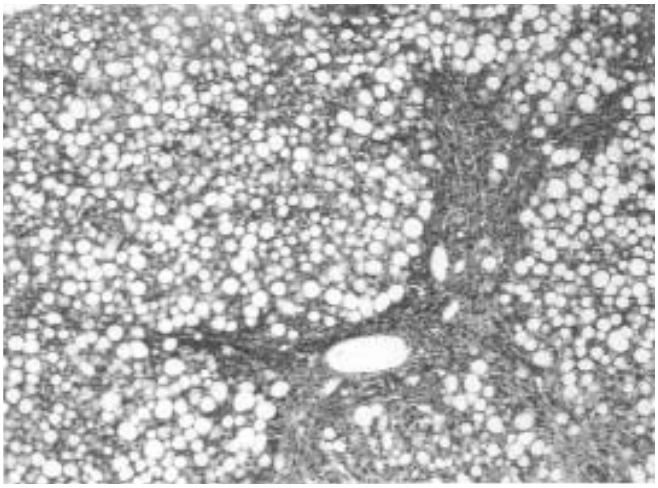

Figure: Liver biopsy showing parenchymal distortion by fibrosis with macrovesicular fatty change and the presence of Mallory's hyaline in keeping with steatohepatitis.

DISCUSSION

Prior to the availability of HAART, HIV-related liver disease was dominated by opportunistic infections and malignancies. Drug hepatotoxicity was related mainly to reactions to sulfonamides for pneumocystis treatment or isoniazid/rifampin used for tuberculous therapy. Co-infection with

hepatotrophic viruses, including Hepatitis B and C were prevalent (4, 7, 8).

Antiretroviral therapy has several undesirable side effects which challenges the management of HIV-infected patients. Liver toxicity is especially important since it often leads to HAART discontinuation (4, 9). The reported incidence of severe liver toxicity with HAART therapy ranges from 2–18% (9). In the United States of America (USA), hepatoxicity secondary to HAART remains the most common cause of deranged liver enzymes and of drug therapy interruption. Figures of HAART discontinuation in the USA have risen from 6% in 1996 to 31.8% in 1999 (9). In the clinical setting, it is often difficult to ascribe the contributions of each drug within a combination to overall hepatotoxicity. In addition, several factors have been identified as risk for severe hepatotoxicity in patients taking ARVs. Alcohol intake, older age and female gender are associated with increased risk. The prior presence of elevation of serum transaminase, previous use of monotherapy or lack of response to HAART are other risk factors (4, 9, 10). Co-existing infection with Hepatitis B and C infection also increases the risk (4).

The non-nucleoside analogue reverse transcriptase inhibitors (nNRTI) can induce direct toxicity in the liver and in addition, hypersensitivity reactions have been reported especially with nevirapine and zalcitabine (9). Icteric hepatitis has been reported also with neviripine (11). In general, severe HAART-related hepatitis is very uncommon, although fatal outcomes due to hepatic failure have been documented (4).

The incidence of hepatotoxic effects of the NRTI is low (4). This class of ARVs acts on the hepatocytes to deplete mitcochondrial DNA synthesis by inhibition of polymerase gamma. This disrupts fatty acid oxidation and energy production resulting in anaerobic metabolism, lactic acidosis and triglyceride accumulation causing hepatic steatosis (4, 12). Mitochondrial toxicity is most severe with zalcitabine, followed by didanosine and stavudine. In addition, various NRTI combinations have heightened hepatotoxicity (12).

The overall incidence of significant hepatoxicity with protease inhibitors (PI) ranges from 3.2 – 18% (4, 13–15) and the risk of severe hepatotoxicity was no different to other classes of ARVs (8). Also, the risk of hepatotoxicity seems relatively low with the use of two protease inhibitors. However, ritonavir was associated with a higher incidence of hepatotoxicity and other adverse drug reactions (8).

The pathogenesis of fatty liver is multifactorial and the relationship between triglyceride accumulation within the hepatocytes and infiltration of the liver parenchyma with inflammatory cells characteristic of non-alcoholic steatohepatitis (NASH) is unclear (16). Hepatic steatosis has been reported in early series of patients with AIDS, however poor nutritional status was the presumed aetiology (17, 18). In the index patient, it was reasonable to conclude that steatohepatitis due to HAART (stavudine) was the clinical diagnosis. This was first described in 1980 as a morphological pattern of hepatic injury characterized by predominantly macrovesicular steatosis, a pattern associated with the obese diabetic females with dyslipidaemia (19). This description has been expanded to non-alcoholic fatty liver disease (NAFLD) which refers to a wide spectrum, ranging from hepatic steatosis, NASH, non-alcoholic steatonecrosis, advanced fibrosis and cirrhosis (6, 16, 20). With the advent of HIV infection, a new susceptible population has emerged because of co-infection with hepatitis B and C, lipodystrophy and HAART therapy.

Steatohepatitis was initially thought to have a benign natural history. The index case, however, based on the AIDS Clinical Trials Group (ACTG) definition, had severe hepatotoxicity (4). Histological findings may range from fatty liver alone in type 1 to additional features of lobular inflammation or balloon degeneration in types 2 and 3 respectively. In type 4, the hallmark of either Mallory hyaline or fibrosis is seen (21). In one series, patients followed for an eight-year period showed progression to cirrhosis more commonly in type 4 (26%) compared with type 1 (4%). There was no significant difference in survival between types 1and 2 (five-year survival, 75.6%) compared to types 3 and 4 (5 year survival, 70.9%). However, fewer had liver related deaths in types 1 and 2 compared with 3 and 4. Although the mean transaminase levels were found to be lower in types 1 and 2, there was no difference in AST/ALT ratio among the groups (21).

The reported patient had type 4 NAFLD which is associated with an increased risk of progression to cirrhosis. The temporal association between ARV therapy and the development of the liver disease supports a drug-induced aetiology. In addition, his liver enzymes were normal prior to regular therapy, became abnormal on therapy and withdrawal of the inciting agent resulted in significantly improved biochemical profiles. His long-term clinical status is confounded by his HIV disease and the need for lifelong HAART therapy. Discontinuation of ARVs is recommended if there is a suspicion of hypersensitivity reactions or lactic acidosis. Withdrawal is also recommended if liver decompensation is present. Severe hepatotoxicity, even in the absence of symptoms warrants discontinuation of ARVs (4).

With the increasing complexity of HAART, clinicians need accurate information regarding the risk of drug hepatotoxicity (5, 8). Therefore, physicians should be mindful of the hepatotoxic potential of these agents and monitor liver enzymes in HIV-infected patients on therapy.

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