Nevirapine-Induced Fulminating Hepatitis


Abstract
Nevirapine induced hepatotoxicity is known but fatality is rare. We report a case of a young individual who developed nevirapine (NVP) induced fatal hepatitis without apparent risk factors or preceding rash. Exacerbation of underlying silent chronic liver dysfunction possibly contributed to the fatal outcome. This case stresses the need for careful evaluation, regular monitoring and prompt omission of drug on suspicion of hepatotoxicity. ©

INTRODUCTION
The introduction of combination antiretroviral therapy (cART) has led to significant reduction in morbidity and mortality associated with HIV infection, although with attendant adverse effects.1 Hepatotoxicity has been frequently associated with the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs).1 The etiology of hepatitis in HIV patients on cART is multifactorial and great caution is required when initiating cART to prevent drug induced hepatotoxicity.1

CASE REPORT
A 38 years old non-alcoholic male with high-risk behaviour was diagnosed HIV positive in 2000 during clinical screening for pyrexia of unknown origin (PUO). He was prescribed 9 months of anti-tuberculous treatment (ATT) empirically and regular follow-up thereafter. In December 2005, his HIV-1 viral load was 35,71,428 copies/ml with absolute CD4 count of 272 cells/mm3. He was started on cART comprising Zidovudine (AZT), Lamivudine (3TC) and Nevirapine (NVP), without any co-medications. His liver functions then were normal. Three weeks after initiation, he developed fever, abdominal pain, nausea, vomiting and watery diarrhoea; 24 hours after which he developed oliguria and was hospitalized. On examination, mild icterus and dehydration were the only positive findings. Investigations showed a marked increase in hepatic transaminase, markers for viral hepatitis were negative and stool examination was normal (Table 1). Abdominal ultrasound revealed hepatomegaly, fatty infiltration, gall bladder wall thickening, bulky pancreas and moderate ascites. cART was withheld and intravenous antibiotics and hepatoprotectives were administered. However, oliguria worsened and he was transferred to the critical care unit, with subsequent development of anuria, deranged coagulation profile and resistant hypovolemic shock. He progressively deteriorated and succumbed on the 3rd day, despite ventilatory support.

DISCUSSION
Nevirapine administration in HIV-infected patients has been associated with severe, potentially life-threatening skin reactions and hepatotoxicity.2 Identified risk factors for developing hepatotoxicity with nevirapine are female gender, chronic hepatitis C/B virus co-infection, a CD4 count ≥ 250 cells/mm3 in women and ≥ 400/mm3 in men, and abnormal baseline transaminase levels.3 The period of highest risk is the initial 4 weeks. The majority of symptomatic events are mild and improve after stopping the drug. The cause may be immunoallergic (within 18 weeks of initiation) or an intrinsic toxic drug effect (after 18 weeks).4 Symptoms of hepatitis include fatigue, malaise, nausea, abdominal discomfort, and jaundice. These may be preceded by skin rash by an average of 13 days, but the relationship between the two is unclear.4 An increase in transaminase levels is the first sign and the incidence of asymptomatic increases in hepatic transaminases is approximately 5-15%.4 Clinically symptomatic hepatitis is found in approximately 1%, but acute hepatic failure is rare (0.1%).5 Nevirapine should be discontinued when transaminase levels are raised to 5 times the upper limit; or in the presence of rash or clinical hepatitis.5 Liver transplantation may be life-saving.

The possible causes of acute fulminant hepatitis in our patient were antiretroviral drug toxicity or acute viral hepatitis due to hepatitis viruses (A, E), cytomegalovirus (CMV) or Epstein-Barr virus (EBV). Amongst cART, 3TC
is not hepatotoxic and AZT causes steatohepatitis after a few months.\textsuperscript{1} Viral markers for hepatitis A or E were absent and hepatitis due to CMV or EBV is unlikely at CD4 count of 272 cells/mm\textsuperscript{3}. Thus, NVP was the most likely culprit. The early development of moderate ascites suggested underlying chronic non-alcoholic fatty liver disease (NAFLD), supported by presence of steatosis and hepatomegaly. Fulminant hepatitis in this low risk individual was possibly due to worsening of underlying NAFLD with superadded NVP-induced hepatotoxicity.

**REFERENCES**


