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Case Report

Boosting Dose of Ritonavir as a Cause of Widespread Hepatic Macrovesicular Steatosis

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Abstract

This is a case of a widespread hepatic steatosis in an HIV positive lady which began since commencing a booster dose of ritonavir. Vigilance is needed in interpreting liver ultrasounds showing fatty infiltration and the cause determined.

Introduction

It is well documented that combination antiretroviral therapy (cART) can cause a range of lipid and adipose tissue abnormalities as part of lipodystrophy which include fat redistribution, insulin resistance and dyslipidaemia [1]. Non alcoholic fatty liver disease is not uncommon in HIV infection [2,3] and hepatic steatosis is a recognised side effect of many drugs comprising cART although the benefits on the liver outweigh the side effect profile [3,4]. Ritonavir is commonly used as a sub-therapeutic 'booster' drug for increasing levels of other protease inhibitors to enable tolerable treatment levels. Macrovesicular hepatic steatosis is most commonly caused by obesity and excessive alcohol intake, and is unlike the microvesicular pattern seen in mitochondrial toxicity [4,5].

Case Report

A 63 year old Caucasian lady was admitted in 2011 with decreasing oral intake, poor mobility progress and confusion after a recent fracture neck of femur and subsequent hemiarthroplasty. She was diagnosed with HIV in 2004 and was thought to have acquired this from a bisexual partner. There was a past medical history of treated non-Hodgkin's lymphoma, cerebrovascular accident, asthma, glucose intolerance, previous excessive alcohol intake, pulmonary TB, L1 vertebral collapse, pneumonia, bilateral cataracts and iron deficiency anaemia. Liver ultrasound scans and liver function tests had been normal. There was no hepatitis B or C co-infection. Her CD4 count on admission was 660 and her HIV viral load was <50 copies/ml.

Her initial cART regime had had to be changed: combivir (raised lipids), efavirenz (depression), kivexa (intolerance and resistance), nevirapine (concomitant anti-TB therapy), tenofovir/didanosine/lamivudine (resistance) and etravirine (peripheral neuropathy). The regime for the recent two years was atazanavir 300mg once daily, ritonavir 100mg once daily (boosting dose), raltegravir 400mg twice daily and maraviroc 150mg twice daily. She was also commenced on spironolactone to help with leg oedema.

Approximately 1 year after commencing this cART regime, she developed right upper quadrant pain with distension. Her AST was 38 IU/l, gamma GT 28 IU/l, alkaline phosphatise 73 IU/l, total bilirubin 30 umol/l, total protein 57 g/l and albumin 25 g/l. The liver ultrasound was reported as 'enlarged in size with changes in echotexture suggestive of liver parenchymal disease'. This lady denied drinking alcohol for over 10 years and her LFTs normalised over the next 6 months (the also family confirmed lack of alcohol intake). Metformin was commenced for glucose intolerance and pravastatin 40mg once daily for raised fasting lipid levels. There were no physical signs of lipodystrophy and she had a dietitian review for high lipids and low vitamin D levels. Citalopram was also commenced as an antidepressant and due to increasing falls, loss of consciousness, incontinence and tongue-biting, lamotrigine was started for epilepsy as a possible post stroke

effect. A repeat CT scan of her abdomen with contrast showed diffuse hypo-attenuation of hepatic steatosis.

On this final admission, due to ongoing nausea, vomiting, constipation and poor oral intake this lady was found to have a bleeding gastric ulcer on endoscopy and despite initially improving, this lady had an asystolic cardiac arrest and died despite resuscitation attempts. Hypokalaemia was noted at the time of arrest.

At autopsy, the patient was slim with a BMI of 22.1. The liver was enlarged (1914gm) and although grossly it looked cirrhotic, histopathology (Figure 1) showed severe macrovesicular steatosis and cholestasis, without fibrosis or hepatitis. There was also osteoporosis, pancreatic atrophy, apical lung scarring, tongue candidiasis and thyroid atrophy. There was no recurrent lymphoma, TB, HIV-encephalitis or chronic pancreatitis.

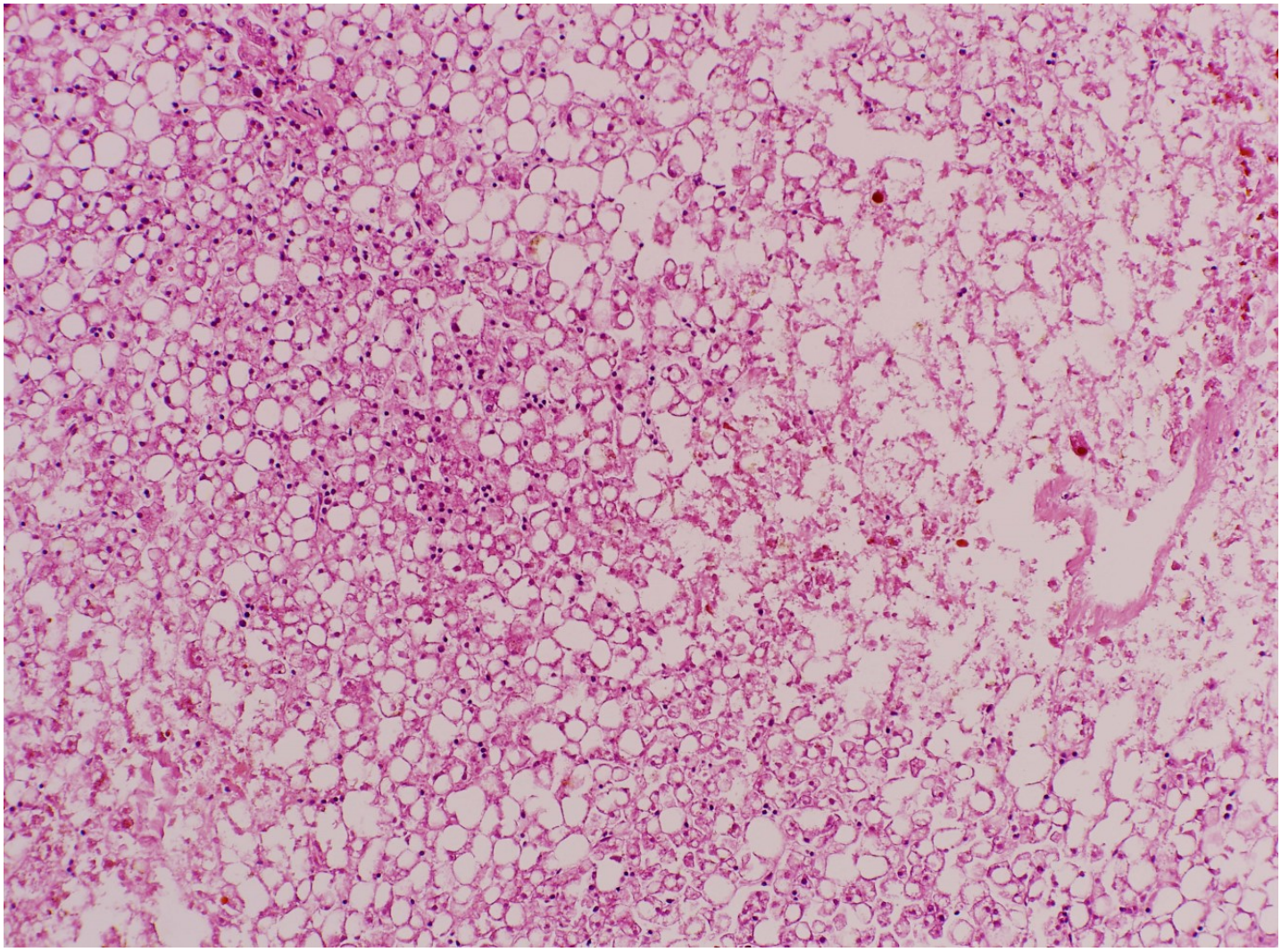

Figure 1. Liver histopathology at autopsy. There is severe macrovesicular steatosis but no hepatitis or fibrosis (H&E).

Discussion

The cause of death was metabolic failure exacerbated by liver steatosis - caused by ritonavir. Atazanavir is not regarded as causing changes in lipids or lipodystrophy [6]. Raltegravir and maraviroc do not cause steatosis [7]. Although insulin resistance is associated with non-alcoholic hepatic steatosis [1], the lack of central obesity goes against this. HIV viraemia and diabetes is associated with significant fibrosis [8] which was not seen in this lady.

To our knowledge, this is a first case of a booster dose ritonavir causing a very widespread hepatic macrosteatosis without causing fibrosis or inflammation [7,9] and is probably exacerbated by HIV and the ageing process. This case has been formally reported to the UK Medicines and Healthcare Regulatory Agency as recommended by HM Coroner at the inquest.

Conclusion

This is the first documented case of a boosting dose of antiretroviral therapy being responsible for causing a widespread macrovesicular steatosis to my knowledge. More vigilance is needed in ascertaining drug related toxicity in cases where intensive investigations in an unwell patient fail to conclude a diagnosis.

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