Case Report

Reactivation of the Epstein–Barr Virus Leading to Acute Liver Failure in a Patient Living with HIV

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Abstract

We report a case of a 46-year-old female living with HIV since 2010 who was originally from Malawi and had settled in the UK in 2001. She was admitted to our hospital with confusion and quickly noted to have a decreased Glasgow Coma Scale of 10/15. Her biochemical parameters showed the presence of elevated liver function tests (LFTs), clotting abnormalities, and her ammonia were found to be >400 mmol/L with a severe metabolic acidosis (pH = 7.05). She was treated for HIV with combined antiretroviral therapy, namely tenofovir disoproxil fumarate, emtricitabine (FTC) and cobicistat boosted atazanavir 2 years previously and had normal LFTs at that time. Her HIV-1 viral load was 1400 copies/ml on admission after recently having an undetectable viral load 2 months previously, and her CD4 count was 480. Her relevant past medical history included insulin-dependent diabetes mellitus. Her other medications included insulin, ramipril, sertraline, amitriptyline, and zopiclone. Toxicology and viral hepatitis screen were negative. Epstein Barr virus (EBV) serology showed evidence of previous exposure, but she was found to have a very high EBV viral load of 55,000 copies/ml, which given her serology, was very likely to be a reactivation of EBV infection rather than a primary EBV infection. In the intensive care unit, the patient deteriorated and died very quickly. The postmortem examination showed extensive hepatic necrosis with collapse. To our knowledge, this is the first case report to show an association between EBV reactivation and fulminant hepatic failure in an individual living with HIV.

Keywords: Acute liver failure, Epstein–Barr virus, HIV

Introduction

The liver is a vulnerable organ for people living with HIV (PLWHIV) as raised liver function tests (LFTs) can be due to many causes, which is attributed to different mechanisms of injury. A summary of these factors are shown in Table 1. For instance, fatty liver and other liver pathology such as viral hepatitis, alcohol, and HIV medication may induce liver damage through the excess release of oxidative stress and exacerbate the process of liver inflammation and fibrosis.[1,2] The hepatic injury through immune reconstitution inflammatory syndrome (IRIS), is more unique to HIV. IRIS can be described as a worsening of the current HIV infection or the emergence of other new infections after starting treatment with highly active antiretroviral treatment.[3] New infections can be like hepatitis B and C and occasionally can be Epstein Barr virus (EBV). For instance, it was estimated that in PLWHIV, around 5%–25% of patients might be coinfected with hepatitis B virus (HBV), 2 30% with hepatitis C virus.[4] Other potential mechanisms that can be involved in liver injury with HIV are mitochondrial toxicity, systemic inflammation, and accumulation of toxic metabolites.[5] Liver injury with HIV become an important issue as it was estimated that 13%–18% of all-cause mortality in HIV-infected can be related to liver disease.[6,7] Importantly, fatty liver can be associated with excess production of free fatty acids, and this in the combination of HIV medication or concomitant hepatitis, can lead to lipotoxicity.[8] Importantly, 30%–40% of PLWHIV may have developed features or signs related to nonalcoholic fatty liver disease.[9,10] In this

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case report, we attempt to explain the association between idiopathic acute liver failure (ALF) in a patient living with HIV and reactivation of EBV.

Case Report

This 46-year-old female diagnosed with HIV in 2010 and was treated with effective combined antiretroviral therapy. She was treated with insulin for diabetes, and she was also known to have a history of HBV, hypertension, obesity, and the history of overdose. She was admitted to our hospital with an increased confusional state. During admission to hospital, she deteriorated, and this was associated with decreased Glasgow coma scale (GCS) 10/15. She was admitted to the department of critical care and was found to have ALF, acute kidney injury, and a coagulopathy. A summary of her biochemical and virology investigations can be found in Table 2. A computed tomography (CT) scan of her brain, chest, abdomen, and pelvis was unremarkable, specifically demonstrating a normal liver texture with normal biliary dilation [Figure 1]. The echocardiogram showed normal left ventricular function and size. Our plan of management was to arrange a transfer to our regional tertiary liver unit. Unfortunately, her GCS did not improve, and the patient died 34 h later after admission to the hospital. A postmortem examination showed acute massive liver necrosis with collapse, particularly in zone 3 with no siderosis or evident inflammatory hepatitis [Figure 2]. There were no A1AT globules, no copper associated protein on orcein stain, no viral inclusion bodies; CD68 immunohistochemistry highlighted the Kupffer cell expansion phagocytosing dead hepatocytes but without hemophagocytosis and no fibrosis was seen. The *in situ* hybridization evaluation for EBV was negative, but since the liver was necrotic autolyzed and the test depends on visualizing EBV in live lymphocytes, this is to be expected.

Table 1: Illustrating possible causes of liver failure in individuals living with HIV

Causes
Paracetamol overdose
HIV medication in particular nevirapine and efavirenz
Viral hepatitis
EBV
Autoimmune hepatitis
Lymphoma

EBV: Epstein–Barr virus

Table 2: Biochemical and virology investigations

Biochemical investigations	Value	Virology investigations	Value
Bilirubin	73 umol/L	EBV VCA IgM	Not detected
		EBV VCA IgG	Detected
		EBV EBNA IgG	Detected
		EBV DNA	55,000 c/ml
		Hepatitis B	Immune
		Hepatitis A	Negative
		Hepatitis C	Negative
ALT	5274 IU/L	Anti-Hbs	>100
Bilirubin	73 umol/L	Consistent with past hepatitis B	
AST	334 IU/L	Hepatitis surface antigen	Not detected
ALP	276 IU/L	HIV viral load	1400 c/ml
pH	7.05	CD4 count	480
Lactate	22 mmol/L	Blood culture	Negative
Bicarbonate	6.3 mmol/L	Sputum culture	*Candida albicans*
Creatinine	511 mmol/L	Autoimmune screen	Negative
GFR	8 ml/min	Toxicology screen	Negative
Urea	16.9 mmol/L	Prothrombin	58.5
HbA1c	13.3%	PT control	12.2

ALT: Alanine transferase, AST: Aspartate transferase, ALP: Alakaline phosphatase, EBV: Epstein–Barr virus, HbA1c: Hemoglobin A1c, GFR: Glomerular filtration rate, VCA: Viral capsid antigen

Discussion

In this case report, the patient's death was due to acute massive liver necrosis (fulminant acute hepatic failure). The history showed she was obese and on insulin therapy for diabetes, and this may raise suspicion of fatty liver. However, virology screen confirmed the evidence of past hepatitis B infection but no reactivation. Her EBV serology showed evidence of previous exposure. However, she was found to have a very high EBV viral load of 55,000 copies/ml which given her serology was very likely to be a reactivation of EBV infection rather than a primary EBV infection. She was admitted to the hospital 3 months before her death with mild confusion, lethargy, and hyponatremia. She was also admitted to the hospital 1-year ago before her death with low-grade fever, delirium, and confusion. At that time, she was investigated extensively, and lumbar puncture showed no abnormalities were seen in the cerebrospinal fluid study , EEG, or CT scan of the head. In view of the high viral load of EBV, she is not fulfilling all the diagnostic criteria for the diagnosis of chronic

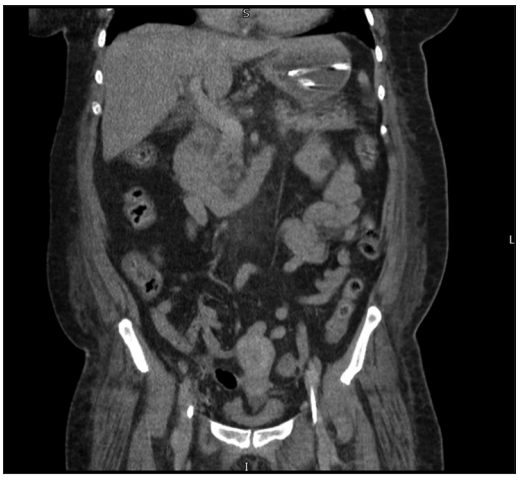

Figure 1: Abdominal computed tomography with the normal contour of the liver (radiology report-liver enhances homogeneously, no focal liver lesion and patent portal vein)

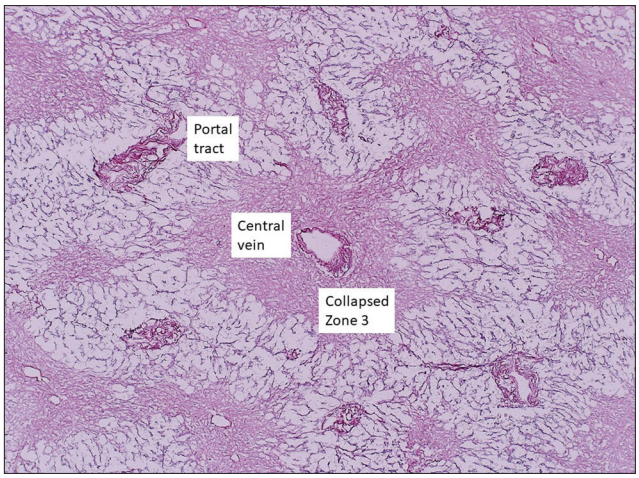

Figure 2: Liver histology (see powerpoint file) showed there was centriacinar (zone 3) necrosis and collapse. The reticulin framework is condensed in this zone. Reticulin stain, medium power

active EBV infection, which can be associated with systemic inflammation and neoplastic disease. These criteria are (1) sustained or recurrent infectiousness mononucleosis-like symptoms for more than 3 months (2) elevated EBV viral load (3) EBV infection in T or natural killer cells (4) exclusion of secondary causes of congenital or secondary causes of immune deficiency.[11] However, several reports showed a close association between EBV and severe liver injury. For instance, Mellinger *et al*. showed that the prevalence of ALF due to EBV was 0.21% (four patients) among the 1887 adult ALF patients enrolled into the US ALF study group from January 1998 to February 2012. Histology for these four patients ranged from cholestasis to sub-massive necrosis with Epstein-Barr encoding region + staining in two of the three samples tested. The overall follow-up of these patients showed that two died of ALF, one underwent liver transplantation (LT) and one survived with supportive care and is well at 5 years. The authors concluded that EBV is associated with a high case fatality rate due to liver failure, and good outcomes may be achieved with a liver transplant.[12] Zhang *et al*. report a case of ALF in an immunocompetent 67-year-old woman caused by EBV infection that was treated by orthotopic LT (OLT). The patient recovered well after the liver transplant without evidence of recurrence of EBV infection.[13] Dumortier *et al*. and Feranchak *et al*. both reported the success of OLT as treatment of ALF caused by EBV infection in immunocompetent young women (2 women).[14,15] Petrova and Kamburov discussed in the review article about the association between EBV and hepatitis and liver cancer in immunocompetent individuals.[16] Several other reports showed that EBV can induce liver failure, especially in the presence of other comorbidities like hepatitis B, A, and hemolytic anemia.[17-19] From the above narration, it is possible to suggest that that the liver was first hit by obesity, fatty liver, diabetes, HIV and previous hepatitis B infection; it is likely that the second hit was with an increase in the titer of viral load of EBV which is possibly of chronic nature.

Conclusion

An activated EBV may have serious consequences in an immunocompromised HIV patient. Therefore, it is advisable to screen for active EBV in all patients with HIV presenting with abnormal LFTs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol 2017;14:397-411.
2. Kim HN, Nance R, Van Rompaey S, Delaney JC, Crane HM, Cachay ER, *et al*. Poorly controlled HIV infection: An independent risk factor for liver fibrosis. J Acquir Immune Defic Syndr 2016;72:437-43.
3. Novak RM, Richardson JT, Buchacz K, Chmiel JS, Durham MD, Palella FJ, *et al*. Immune reconstitution inflammatory syndrome: Incidence and implications for mortality. AIDS 2012;26:721-30.
4. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558-67.
5. Sherman KE, Peters MG, Thomas D. Human immunodeficiency virus and liver disease: A comprehensive update. Hepatol Commun 2017;1:987-1001.
6. Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, Law M, *et al*.; Data Collection on Adverse Events of Anti-HIV drugs (D: A: D) Study Group. Factors associated with specific causes of death amongst HIV-positive individuals in the D: A: D Study. AIDS 2010;24:1537-48.
7. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, *et al*. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D: A: D): A multicohort collaboration. Lancet 2014;384:241-8.
8. Mastroianni CM, Lichtner M, Mascia C, Zuccalà P, Vullo V. Molecular mechanisms of liver fibrosis in HIV/HCV coinfection. Int J Mol Sci 2014;15:9184-208.
9. Ahmed MH, Husain NE, Malik A, Woodward C, Mital D. Non-alcoholic fatty liver disease and HIV/AIDS: A new way of modulation of cardiovascular risk. AIDS Rev 2017;19:190-7.
10. D Mital R. Boosting Dose of Ritonavir as a Cause of Widespread Hepatic Macrovesicular Steatosis. J J Gastro Hepato 2018;5:031.
11. Arai A. Advances in the study of chronic active Epstein-Barr virus infection: Clinical features under the 2016 WHO classification and mechanisms of development. Front Pediatr 2019;7:14.
12. Mellinger JL, Rossaro L, Naugler WE, Nadig SN, Appelman H, Lee WM, *et al*. Epstein-Barr virus (EBV) related acute liver failure: A case series from the US Acute Liver Failure Study Group. Dig Dis Sci 2014;59:1630-7.
13. Zhang W, Chen B, Chen Y, Chamberland R, Fider-Whyte A, Craig J, *et al*. Epstein-Barr virus-associated acute liver failure present in a 67-year-old immunocompetent female. Gastroenterol Res 2016;9:74-8.
14. Feranchak AP, Tyson RW, Narkewicz MR, Karrer FM, Sokol RJ. Fulminant Epstein-Barr viral hepatitis: Orthotopic liver transplantation and review of the literature. Liver Transpl Surg 1998;4:469-76.
15. Dumortier J, Mekki Y, Rimmelé T, Ber C, Maillard E, Fafi-Kremer S,

et al. EBV-induced fulminant hepatic failure: Favorable outcome after liver transplantation. Gastroenterol Clin Biol 2007;31(Pt 1):725-8.
16. Petrova M, Kamburov V. Epstein-Barr virus: Silent companion or causative agent of chronic liver disease? World J Gastroenterol 2010;16:4130-4.
17. Pinto-Patarroyo GP, Rytting ME, Vierling JM, Suarez-Almazor ME. Haemophagocytic lymphohistiocytosis presenting as liver failure following Epstein-Barr and prior hepatitis a infections. BMJ Case Rep 2013;2013. pii: Bcr2013008979.
18. Palanduz A, Yildirmak Y, Telhan L, Arapoglu M, Urganci N, Tüfekci S, *et al*. Fulminant hepatic failure and autoimmune hemolytic anemia associated with Epstein-Barr virus infection. J Infect 2002;45:96-8.
19. Jiménez-Sáenz M, Pérez-Pozo JM, Leal-Luna A, Herrerías-Gutiérrez JM. Lethal liver failure in an elderly patient with hepatitis B superinfected with Epstein-Barr virus. Eur J Gastroenterol Hepatol 2002;14:1283-4.