

Case Report

Fatal Hepatitis B Infection Despite Immunization in an HIV-infected Infant: A Possible Case of Vaccine Failure and Immune Reconstitution Inflammatory Syndrome

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Summary

We report a case of hepatitis B immune reconstitution inflammatory syndrome in an 8-month-old girl with *Mycobacterium tuberculosis* complex and human immunodeficiency virus (HIV) co-infection. In resource-constrained countries, HIV-hepatitis B co-infections are often difficult to diagnose and to treat. We highlight on the importance of hepatitis B and HIV screening in pregnant women, to implement efficient preventive measures.

Key words: paediatric HIV, hepatitis B, co-infection.

Introduction

Hepatitis B virus (HBV) infection is a worldwide health problem, which can lead to acute hepatic failure, chronic hepatitis, liver cirrhosis and cancer. In endemic areas such as Africa, Asia and the Southern part of Central and Eastern Europe, paediatric HBV

infection occurs through perinatal or horizontal transmission during infancy and childhood [1, 2]. HBV and human immunodeficiency virus (HIV) co-infection is common with prevalence rates of 10–20% [3–5]. In South Africa, immunization against HBV at 6, 10 and 14 weeks of age has been part of the Expanded Program on Immunization, since 1995 [6].

Combination anti-retroviral therapy (cART) has dramatically improved the outcome of HIV-infected children. However, in resource-constrained countries, the diagnosis of HIV infection is often made late, delaying initiation of cART. Many children are exposed to and infected with opportunistic infections prior to starting cART and are therefore at increased risk of immune reconstitution inflammatory syndrome (IRIS).

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Case Report

We report an 8-month-old girl with concomitant HIV and HBV infections and possible IRIS. On initial presentation at 8 months of age, she had stage IV HIV disease characterized by right axillary lymphadenitis, oral thrush, hepatosplenomegaly, severe failure to thrive (weight 4.3 kg; 54% of expected

weight for age; length 58 cm; 84% of expected length for age) and probable HIV encephalopathy (delayed milestones and microcephaly). Presence of a Bacille Calmette-Guérin (BCG) vaccination scar was noticed on the right deltoid.

Her CD4 percentage was severely depleted at 0.78% and her viral load was 690 000 copies of HIV RNA per millilitre. HIV infection was confirmed in her mother who had an absolute CD4 count of 44 cells mm^{-3} .

A right axillary lymph node aspirate showed acid-fast bacilli and the culture was positive for multi-sensitive *Mycobacterium tuberculosis* complex, not further speciated into *M. tuberculosis* or BCG.

Cotrimoxazole prophylaxis was prescribed and tuberculosis (TB) therapy with daily isoniazid 20 mg kg^{-1} , rifampicin 20 mg kg^{-1} , pyrazinamide 40 mg kg^{-1} and ethambutol 20 mg kg^{-1} commenced. Seven weeks later, cART with zidovudine, lamivudine, lopinavir/ritonavir boosted with additional ritonavir was started.

After 6 weeks on cART, she developed acute liver failure with hepatic encephalopathy (altered mental status, hepatic flap and seizures). While her baseline liver function tests had been normal, alanine aminotransferase (ALT) had increased to 2418 IU l^{-1} ; total bilirubin to 269 mmol l^{-1} (direct bilirubin 112 mmol l^{-1}); lactate dehydrogenase (LDH) to 2942 IU l^{-1} . Coagulopathy was present with an INR > 10, prothrombin time > 120 s and partial thromboplastin time 127 s. An ammonia level could not be done. A CT scan of the brain showed cerebral oedema but no haemorrhage. Cerebral spinal fluid showed 420 lymphocytes mm^{-3} with a normal protein (0.34 g l^{-1}), normal glucose (3.3 mmol l^{-1}) and negative cultures for bacteria and *M. tuberculosis* (on Lowenstein-Jensen medium).

Toxicity to treatment was suspected and both HIV and TB treatment were discontinued. Supportive treatment for liver failure was provided (fresh dried plasma, vitamin K, lactulose, fluid management, control of seizures and of hypoglycaemia). Hepatitis serology revealed a positive surface Ag, core IgM and hepatitis B e Ag (HBeAg). Her CD4 level had increased to 6.6% and her viral load had dropped to 13 000 copies ml^{-1} (1.7 log drop) showing a good biological response to cART. Her mother's blood was positive for hepatitis B surface Ag (HBsAg). Review of the immunization record revealed that the infant had received HB vaccine (Heberbiovac HB) 10 μg (0.5 ml) at 6, 10 and 14 weeks of life.

One month later, after slight improvement of the liver function (ALT 107 IU l^{-1} , total bilirubin 158 mmol l^{-1} (direct bilirubin 92 mmol l^{-1}) and INR 1.63), non-hepatotoxic anti-TB drugs (ciprofloxacin, amikacin and ethambutol) were restarted one by one and thereafter cART was reintroduced. Subsequently, isoniazid and rifampicin were recommenced while closely monitoring her liver function.

Unfortunately, the liver function deteriorated. She had a persistent coagulopathy requiring multiple blood and fibrinogen degradation product transfusions and daily vitamin K injections. Despite reverting to less hepatotoxic anti-TB drugs again, the infant finally died 3 months later. The terminal event was linked to liver failure along with a severe diffuse bleeding. Worsening of her right axillary lymphadenitis was also noticed 10 days prior to this fatal event after 5 months of cART. Hilar lymph nodes and bilateral patchy changes were present on chest X-ray. Post-mortem biopsies showed cirrhosis of the liver without granulomas and granulomatous lesions in the lymph node. Auramin stain and mycobacterial culture were negative. Percentage of CD4 was 6.5% at this time.

Discussion

Hepatotoxicity is common after initiation of cART in HIV-infected patients. In a recent African cohort study, hepatotoxicity generated minimal morbidity and was rarely fatal, but concomitant TB therapy and HBsAg significantly increased the risk of hepatotoxicity. Our patient had both the risk factors for hepatotoxicity [7]. The management of this infant was extremely difficult because of co-infection with TB, HIV and HBV. Reported experience in the treatment of such co-infected patients is limited. TB is life threatening under these circumstances; hence, the early use of non-hepatotoxic anti-TB drugs is recommended. After stabilization, cART was reintroduced and lamivudine could have had an impact on the HB infection. However, after suppression of HBV replication by lamivudine, some individuals with may develop breakthrough HBV replication following development of point mutations giving lamivudine resistance; this may lead to hepatic inflammation and transaminase elevation [8]. Moreover, lamivudine monotherapy is associated with a high rate of viral resistance. Combination with tenofovir reduces incidence of resistance. Unfortunately, adequate formulation and dosing of tenofovir are not yet available for children and it is only approved above 18 years of age [9].

Whether the child was infected with HBV through vertical or horizontal transmission is unknown, but most probably infection occurred vertically. HIV-related immune suppression leads to increase in the HBV viral load [10], thereby increasing the risk of transmission from mother to child. HBV screening is not part of antenatal care in South Africa and there is a need for data on co-infection in pregnancy. Correct identification of HBV infection antenatally will allow for HBV hyperimmune gamma globulin and the first dose of the HBV vaccine at birth. Change in the South African immunization calendar by introducing the first dose of HBV vaccine at birth could already have a positive impact on vertical

transmission [11]. In the less probable figure that the child horizontally acquired HBV after receiving three documented immunizations we could hypothesize HBV vaccine failure. This could be problematic in settings with a high prevalence of severely immunocompromised children. The lack of response to HBV vaccine in HIV-infected children is worrying [12] although a potentially better response is anticipated in infants on cART [13].

We postulate that our patient developed IRIS to HBV and BCG. The timing of liver failure, 7 weeks after initiating cART and the enlarging right axillary nodes after 3 months, together with evidence of virological and immunological response to cART are supportive of this.

We cannot differentiate if her lymphadenitis was due to BCG and not TB. Indeed, cultures cannot differentiate between *Mycobacterium bovis* and *M. tuberculosis*. Polymerase chain reaction speciation was not feasible in our setting. Despite anti-TB treatment, also active against *M. bovis*-BCG, and apparent response to cART, the right axillary lymphadenitis worsened and granulomas were found at autopsy. Although auramin stain and mycobacterial culture were negative, both TB and BCG IRIS are possible as cultures can be sterile in paradoxical IRIS due to improved cell-mediated immunity, augmented by treatment [14]. Right axillary adenitis is common in BCG IRIS as the lymphatic drainage from site of intra-dermal inoculation over the right deltoid drains to this area [15]. In South Africa, 71% of paediatric IRIS is caused by BCG [16]. The adenitis noted at baseline probably reflects regional BCG-osis, although disseminated BCG, was possible in this highly immunocompromised infant. However, the liver biopsy did not show granulomas and *M. tuberculosis* complex was not isolated from gastric washings.

This case highlights some of the consequences of delaying the initiation of cART in resource-constrained countries and the urgent need for early diagnosis and treatment of HIV in infants to reduce mortality and morbidity including IRIS [17] and to improve response to immunization.

Data are scarce on HBV-HIV-1 co-infections in Africa [18] notably among children [19]. In a paediatric cohort from Cote d'Ivoire, 12.1% were HBsAg positive at baseline, of whom, 84% were also HBeAg positive, the latter, with HIV are risk factors for chronic HB [20]. As cART rolls out in Africa, we need to consider HBV endemicity.

The strengthening of public health strategies to improve the prevention of mother-to-child transmission of HIV and HB in endemic countries is crucial.

To our knowledge, this is the first report of possible HB IRIS in a HIV-infected child concurrent with *M. tuberculosis* complex. The management of such cases is extremely complex. Prevention is simpler.

References

1. Leung N. Chronic hepatitis B in Asian women of childbearing age. *Hepatol Int* 2009; 3(Suppl 1):24–31.
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; 11:97–107.
3. Lee HC, Ko NY, Lee NY, *et al.* Seroprevalence of viral hepatitis and sexually transmitted disease among adults with recently diagnosed HIV infection in Southern Taiwan, 2000–2005: upsurge in hepatitis C virus infections among injection drug users. *J Formos Med Assoc* 2008;107:404–11.
4. Nyirenda M, Beadsworth MJB, Stephany P, *et al.* Prevalence of infection with hepatitis B and C virus and coinfection with HIV in medical inpatients in Malawi. *J Infect* 2008;57:72–7.
5. Diop-Ndiaye H, Touré-Kane C, Etard JF, *et al.* Hepatitis B, C seroprevalence and delta virus in HIV-1 Senegalese patients at HAART initiation (retrospective study). *J Med Virol* 2008;80:1332–6.
6. South African vaccination and immunisation centre. <http://www.savac.ac.za/disease.php?sub3=90>. (17 November 2009, date last accessed).
7. Hoffmann CJ, Charalambous S, Thio CL, *et al.* Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007;21:1301–8.
8. Liaw YF, Chien RN, Yeh CT, *et al.* Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999;30:567–72.
9. National Institutes of Health. Guidelines for the use of Antiretroviral Agents in Paediatric HIV Infection. February 23, 2009. <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf> (17 November 2009, date last accessed).
10. Gilson RJ, Hawkins AE, Beecham MR, *et al.* Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS* 1997;11:597–606.
11. Ekra D, Herlinger K-H, Konate S, *et al.* A non-randomized vaccine effectiveness trial of accelerated infant hepatitis B immunization schedules with a first dose at birth or age 6 weeks in Côte d'Ivoire. *Vaccine* 2008;26:2753–61.
12. Fernandes SJ, Shlessarenko N, Souto FJ. Effects of vertical HIV infection on the persistence of anti-HBs after a schedule of three doses of recombinant hepatitis B vaccine. *Vaccine* 2008;26:1032–7.
13. Pippi F, Bracciale L, Stolzoli L, *et al.* Serological response to hepatitis B virus vaccine in HIV-infected children in Tanzania. *HIV Med* 2008;9:519–25.
14. Boulware DR, Callens S, Pahwa S. Pediatric HIV immune reconstitution inflammatory syndrome. *Curr Opin HIV AIDS* 2008;3:461–7.
15. Nuttal JJ, Davies MA, Hussey GD, *et al.* Bacillus Calmette-Guerin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy. *Int J Infect Dis* 2008;12:e99–e105.
16. Smith K, Kuhn L, Coovadia A, *et al.* Immune reconstitution inflammatory syndrome among HIV-infected

- South African infants initiating antiretroviral therapy. *AIDS* 2009;23:1097–107.
17. Violari A, Cotton MF, Gibb DM, *et al.* Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008;359:2233–44.
 18. Modi A, Feld J. Viral hepatitis and HIV in Africa. *AIDS Rev* 2007;9:25–39.
 19. Nacro B, Dao B, Dahourou H. HBs antigen in children with suspicion of HIV infection. *J Trop Pediatr* 2001;47:303–4.
 20. Rouet F, Chaix ML, Inwoley A, *et al.* Frequent occurrence of chronic hepatitis B virus infection among West African HIV type-1-infected children. *Clin Infect Dis* 2008;46:361–6.