

# Cholestatic Fibrosing Hepatitis and Hepatitis B after Bone Marrow Transplantation

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## Summary

In the setting of transplantation and chronic hepatitis B viral infection there is a unique histological feature termed cholestatic fibrosing hepatitis. The use of nucleoside analogues in the treatment of this condition has been successful. We describe a case of cholestatic fibrosing hepatitis, which occurred after intense immunosuppression for graft versus host disease in a patient with bone marrow transplantations. She was commenced on lamivudine therapy and showed good clinical, biochemical and virological response. However she succumbed due to sepsis.

**Key Words:** Cholestatic Fibrosing Hepatitis, Hepatitis B viral infection, lamivudine

## Introduction

KGH was a 34 year old lady who presented with jaundice, tea coloured urine and lethargy in August 1999.

Her clinical history dated back to 1996 when she presented with acute myeloid leukaemia. She responded to chemotherapy and during her first remission underwent an allogenic peripheral blood stem cell transplant in Australia. Her immediate post transplant course was unremarkable and she remained well in the first post transplant year. However she subsequently developed chronic graft versus host disease (GVHD), which involved her eyes, skin and lungs. Her respiratory involvement was particularly severe resulting in bronchiolitis obliterans which was progressive, and as implied by the term leads to obliteration of the airways.

This resulted in gradual and relentless decline in her exercise tolerance. Her latest peak flow was 150 l/min in August 1999.

She was on multiple medication including prednisolone, cyclosporin, thalidomide, cotrimoxazole, erythromycin and fluconazole. At the time of her recent presentation, her prednisolone had been tapered down since February 1999.

She had blood transfusions during her initial presentation of acute myeloid leukaemia in 1996.

In 1990 she was HBsAg negative and anti HBe positive. Similar results were observed in 1998. There was no history of previous hepatitis B vaccination. Her mother was HBsAg positive while all her siblings had been vaccinated for hepatitis B.

This article was accepted: 2 October 2001

Clinically she was jaundiced and had a Cushingoid appearance. Her blood pressure was 140/100. There were no of stigmata of chronic liver disease. The liver was only just palpable and was firm in consistency with a smooth edge.

Investigations revealed significantly raised alanine transaminase (1600mmol/l) associated with borderline low albumin (30g/l) levels. Viral markers revealed positive HBsAg, positive IgG anti-HBc, positive HBeAg and detectable HBV DNA by PCR (polymerase chain reaction). Ultrasonography revealed a mildly enlarged liver with normal echogenicity. There was no evidence of cirrhosis or portal hypertension.

A liver biopsy was performed confirming reactivation of hepatitis B. The lobular architecture appeared severely disrupted due to widespread presence of a large number of ground glass hepatocytes which were HBsAg positive, intermixed with many nascent regenerative liver cells of smaller size having pseudoacinar formation. Cholestasis was very prominent mostly within the canaliculi of pseudoacinar lumen and in the pigmented macrophages, which were probably iron positive. There was a prominent degree of intercellular fibrosis around the liver cells, and this seemed to be prevalent at the periportal region in patches with intra-acinar extension. These areas demonstrated a high degree of mononuclear cell infiltration as compared with other areas of acinar parenchyma. Moreover ductular proliferation was also evident. Due to periportal involvement, the interface activity (marginal plate erosion) appeared less well defined. There were 4 - 5 portal tracts that were readily identified in the trichrome stain, which showed no significant previous fibroinflammation such as seen generally in longstanding chronic hepatitis. The reticulin stain demonstrated cobweb-like reticulus. There was no bridging, cirrhosis or fatty change. In the portal tract, there was evidence of biliary tract injury, in the form of nuclear pyknosis and cytoplasmic acidophilia of bile duct epithelia. There was also a slight degree of emperipolesis

by polymorphonuclear leucocytes and rarely by lymphoid cells. A small hepatic artery that showed marked intimal sclerosis of significant degree was seen.

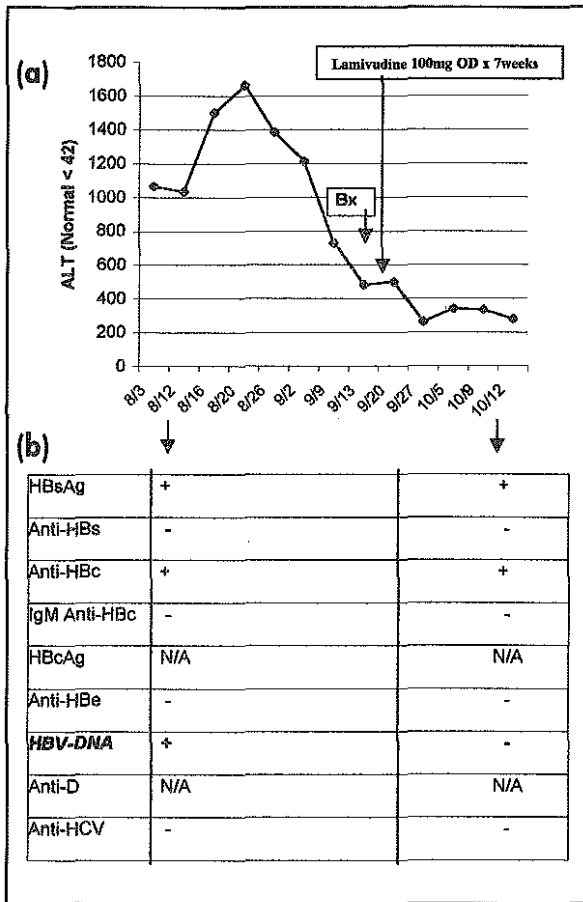
The changes were suggestive of classical cholestatic fibrosing hepatitis (CFH). An Orcein stain for hepatitis B virus was positive. There was no evidence of graft versus host disease, cytomegaloviral hepatitis, herpes simplex hepatitis or drug induced hepatitis. When her liver synthetic function began to show deterioration after 3 weeks of admission, we decided to commence her on specific antiviral therapy to suppress viral replication and thus prevent further deterioration of her liver function.

After the commencement of lamivudine, close monitoring of the biochemical parameters were performed and the serum aminotransferases showed a downward trend.

This was accompanied by restoration of her liver synthetic function with normalization of her prothrombin time and a steady albumin level at 30g/l.

She remained well and her bilirubin which had initially climbed to a high of 400 micromol/l, started to decline after 3 weeks of starting lamivudine. Her alanine transaminase (ALT) dropped from 1600u/L to 250u/L 6 weeks after commencing lamivudine (see Figure 1).

Despite improvement in her biochemical liver profile her overall condition began to deteriorate as she developed sepsis 6 weeks after admission and her graft versus host disease began to flare up. Eventually she succumbed to sepsis and thrombotic thrombocytopenic purpura (TTP), which was evidenced by schistocytes (microangiopathic haemolytic anaemia), evidence of haemolysis in the full blood picture and convulsions. The source of sepsis was not apparent and repeated septic screening did not culture any organisms.



**Fig. 1:** (a). Alanine Transaminase levels before and after the commencement of lamivudine on 25/08/1999 and (b) corresponding changes in virological markers before and after treatment.

This complication occurred 8 weeks after she was commenced on definitive antiviral therapy. Her repeat virological markers revealed the disappearance of HBV DNA by PCR (Figure 1). The HBeAg and HBsAg remained positive and there was stabilisation of her synthetic function.

**Discussion**

This case reveals the outcome of an immunosuppressed individual in whom the Hepatitis B virus was reactivated manifesting itself with jaundice and raised liver enzymes. The reason for this reactivation could be related to the withdrawal of prednisolone and the ongoing immunosuppression, which is a recognized possibility. It is likely that her hepatitis B was acquired perinatally. The other albeit less likely possibility is blood transfusion that she had received in the past.

The viral load showed reduction after 6 weeks of treatment with lamivudine, evidenced by the disappearance of serum HBV DNA by PCR. The histology was very complex and highly impressive. High degrees of viral antigenic expression were seen in the hepatocytes<sup>1</sup>, a feature occurring in patients on immunosuppressive therapy and with the use of corticosteroids. The chronic HBV liver changes in the ordinary form of portal and periportal fibro inflammatory process are less obvious. No bridging necrosis was seen to suggest an acute or subacute bridging necrolytic process. In the setting of transplantation and chronic hepatitis B viral infection there is a unique histological feature that has been described by Davis SE *et al*<sup>2</sup>, which has been termed cholestatic fibrosing hepatitis (CFH). The periportal fibrosing change seen in this case fits well with the disease entity of CFH.

Whether viral mutation may account for such manifestation is unclear. There is an element of regeneration that is evidenced by the intermixed presence of crowded small size liver cells in pseudo-acinar features, and by the expansion of the reticulin framework. Siderotic changes are related to transfusions. Whether this may add an additional oxidative stress and hepatobiliary injury is speculative. The presence of biliary epithelial and hepatic arterial changes is entirely compatible with the Graft versus Host reaction.

Necroinflammatory activity, as evidenced by reduction in alanine transaminase levels (ALT's) also dropped significantly after the commencement of lamivudine. However the serum ALT failed to normalize completely most probably due to interplay of several factors including drug related hepatotoxicity, sepsis and GVHD.

It is imperative that prednisolone withdrawal in chronic hepatitis B patients and those on long term prednisolone therapy be done gradually to prevent Hepatitis B flare due to reactivation. In the setting of borderline liver dysfunction, viral reactivation can have devastating effects as hepatic decompensation can occur and this may be life threatening.

In an individual with immunosuppression, lamivudine therapy will have to be continued for prolonged periods and even indefinitely as withdrawal can result in reactivation of the virus, which may lead to decompensation and life threatening complications. In patients known to have chronic hepatitis B infection, there may also

be an additional role for prophylactic lamivudine therapy when they are to undergo immunosuppressive therapy. It is recommended that therapy with lamivudine or other appropriate anti-virals be commenced immediately as soon as signs of reactivation become apparent. The use of nucleoside analogues in the treatment of this condition has shown significant success<sup>3</sup>. This patient had developed sepsis due to ongoing intense immunosuppression due to the GVHD, which had resulted in TTP and is a highly fatal condition.

In summary, this immunosuppressed patient had responded to lamivudine therapy, both clinically and biochemically. The serum HBV DNA also disappeared during the follow up analysis after 6 weeks of treatment. However she eventually died of sepsis, multi-organ failure and supervening TTP.

#### Acknowledgement

We would like to thank Prof SN Huang for his contribution in reviewing the histology slides.

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#### References

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