Case Report

Co occurrence of Hepatitis B Virus Infection and Autoimmune Hepatitis with Marked Hepatitis B Virus Replication Following Treatment of Autoimmune Hepatitis

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Abstract: Background: Children have different natural history of Hepatitis B virus (HBV) infection. They commonly develop asymptomatic chronic carrier state which is less frequently seen in adults. We describe a rare case of acute on chronic liver failure (ACLF) in the course of concurrent autoimmune hepatitis (AIH) and HBV infection and replication of HBV following the treatment for autoimmune hepatitis. Case Report: A 15 year old male child presented with jaundice and altered sensorium. Physical examination showed hepatosplenomegaly. The liver function tests were markedly altered. Serology was positive for anti liver kidney microsomal antibody (LKM), hepatitis B surface antigen (HBsAg) and immunoglobulin M (IgM) anti hepatitis B core antigen (HBc Ag). Liver biopsy showed chronic hepatitis with features of acute exacerbation. Patient was started on treatment with azathioprine and prednisolone following which clinical and biochemical improvement was noted. After two years of continued treatment a repeat biopsy performed showed fairly reduced histological activity, but marked replication of the HBV (immunohistochemistry for HBsAg and anti HBcAg showed diffuse cytoplasmic and nuclear positivity respectively). These findings suggest viral replication although the patient was clinically stable. At six months follow-up after the second biopsy and cessation of azathioprine and prednisolone, there were raised liver enzymes and viral load, hence the patient was started on antiviral drug Entecavir to which there was good response and the patient is presently doing well. Conclusion: We describe the rare co occurrence of HBV infection and AIH with marked HBV replication following the treatment for AIH

Key Words: Acute on chronic liver failure, Hepatitis B virus, Autoimmune hepatitis, Liver biopsy.

Introduction: Children have different natural history of Hepatitis B virus (HBV) infection. They commonly have asymptomatic chronic carrier state usually diagnosed incidentally or on epidemiological investigation. On the other hand, acute hepatitis B is a self-limiting disease in adults with activity completely subsiding in 2 to 3 months of onset due to the elimination of the virus. A chronic carrier state is less frequently observed in adults.[1] Autoimmune hepatitis (AIH) is a chronic progressive hepatitis characterized serologically by positive antinuclear antibody (ANA), anti smooth muscle antibody (SMA), anti liver kidney microsomal antibody (LKM) and hypergammaglobulinemia; portal inflammatory cell infiltration (plasmacyte dominant) and piecemeal necrosis on histology.[2,3] AIH is divided into two types: type 1 with ANA and/or ASMA positive and type 2 with LKM antibodies. Acute liver failure is more common in type 2 AIH patients and usually in young and adolescent girls.[4] Concurrent occurrence of HBV infection and autoimmune liver disease is uncommon and reactivation of HBV infection following immunosuppressive treatment for AIH is rarely described [1]. On the contrary, hepatitis A virus and hepatitis C virus precipitating AIH have been reported in the literature.[5-7] As per our literature search, we report the
second case of hepatitis B with concurrent AIH in children and perhaps, the first case of reactivation of HBV infection following immunosuppressive treatment in paediatric age group.

Case Report
A 15 years old male child presented to this hospital with jaundice and altered sensorium. Physical examination showed hepatosplenomegaly. The liver function tests were markedly altered; serum bilirubin was 34.4 mg/dL with a direct fraction of 15.7 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 243 IU/L and 205 IU/L respectively, and serum alkaline phosphatase (SAP) was 855 IU/L. Endoscopy revealed grade 1 esophageal varices. Serologically, the patient was positive for anti LKM, hepatitis B surface antigen (HBsAg) and immunoglobulin M (Ig M) anti hepatitis B core antigen (HBc Ag). However, HBV deoxyribonucleic acid (DNA) was not detectable. Immunoglobulin G (IgG) was elevated. Serum ceruloplasmin and 24 hour urinary copper were 18.8 mg/dl and 18 µg respectively. A diagnosis of acute on chronic liver failure (ACLF) was made in which acute insult was probably due to HBV and the underlying chronic liver disease was attributed to AIH. Liver biopsy showed mild lobular disarray with moderate portal inflammation, interface activity and fibrosis (Fig 1). Portal bridging necrosis, focal parenchymal collapse, prominent ballooning of hepatocytes, rosetting and focal giant cell change was present. Focal intracytoplasmic cholestasis was noted. No fatty change or ground glass hepatocytes were seen. Immunohistochemistry (IHC) was negative for HBsAg and HBcAg. A histological diagnosis of chronic hepatitis with features of acute exacerbation was made. Treatment with azathioprine and prednisolone was started for autoimmune hepatitis following which the liver enzymes were normalised over several weeks. A liver biopsy done at the end of two years of continued treatment as the patient continued to be in clinical and biochemical remission showed a mild portal inflammationFig 2) and no other significant pathology like bridging necrosis or collapse, ballooning, rosetting, fatty change or ground glassing of hepatocytes. But there was cytoplasmic positivity for HBsAg (Fig 3) and marked nuclear positivity for HBcAg (Fig 4) on IHC. In comparison to the first biopsy the inflammatory changes and fibrosis were markedly decreased. However, cytoplasmic immunoreactivity for HBsAg and marked nuclear immunoreactivity HBcAg indicating abundant replication of the virus was noted. A diagnosis of mild chronic hepatitis (HBV related) with marked replication of HBV was made (HBV reactivation); (Ishak modified hepatocyte activity index (HAI) score- 4 and Ishak fibrosis score - 1). Based on these histological findings his immunosuppressives were discontinued. Six months after the discontinuation of immunosuppressives, the patient had elevated aminotransferases (twice the normal value) and elevated viral DNA load (>10^8 IU/µl) on routine testing. Hence he was started on antiviral drug Entecavir at a dose of 0.5mg/day. After 8 weeks of oral nucleoside therapy his aminotransferases had normalized. He continues to be on the therapy with Entecavir till date and is doing well.
Figure 4: Immunohistochemistry for HBsAg (two years post treatment with Azathioprine and Prednisolone) showing cytoplasmic positivity.

Discussion:
Administration of immunosuppressive agents like corticosteroids in HBV carriers with malignancies or autoimmune disorders may be associated with the risk of HBV reactivation.[8] We have described a case of liver failure in the course of AIH exacerbated by concurrent acute HBV infection in a paediatric patient. Autoimmune hepatitis is diagnosed on the basis of typical criteria and the exclusion of other causes of liver disease, including viral infection. In children, it is difficult to apply the generally accepted classification in view of the criteria employed, such as alcohol intake, or the presence of viral infections [Epstein bar virus (EBV), Cytomegalovirus (CMV), Human Herpes virus (HHV-6)], which may initiate autoimmune processes or autoantibody production.[9,10] But in this patient there was clear cut positivity for anti LKM antibody along with elevation of immunoglobulin G which strongly favoured AIH type 2, and at the same time there was positivity for HBsAg and IgM anti HBC Ag strongly indicating acute HBV infection. So this patient had both HBV infection and autoimmune liver disease. It can be analysed that the patient went in to liver failure due to the flare up of the underlying autoimmune liver disease as a result of concurrent acute HBV infection as suggested by the clinical history, serology and liver biopsy. It is important to distinguish between AIH with positive viral infection markers and chronic viral hepatitis with positive autoimmune markers. The majority of the cases in the second category are successfully treated by antiviral drugs as the viral components are predominant.[11] Less commonly, the autoimmune components are predominant and respond well to steroids. In the present case, it appeared that the autoimmune component was predominant and was present in a subclinical stage in the course of which the patient acquired HBV infection. Pointers towards acute hepatitis B infection were raised aminotransferases coupled with positivity for HBsAg; IgM Anti HBC Ag and undetectable HBV DNA. This was further substantiated by absence of ground glass hepatocytes and immunonegativity for HBsAg on liver biopsy. A diagnosis of chronic hepatitis with features of acute exacerbation was made on the biopsy which in the background of positive autoimmune serology and acute HBV infection indicated that the chronic hepatitis was of autoimmune origin exacerbated by acute HBV infection. Since the patient was clinically in failure and diagnosed as ACLF (acute on chronic liver failure), treatment with azathioprine and prednisolone was started to treat the underlying etiology (autoimmune hepatitis). Clinical improvement as well as improvement in the biochemical liver function was observed in subsequent months further substantiating the underlying autoimmune etiology. A follow up liver biopsy for evaluation of immunosuppressive treatment and to look for remission was done at the end of two years and showed marked improvement in histology. However, unlike the previous biopsy which was negative for HBsAg and HBCAg immunostaining, this biopsy showed immunopositivity for HBsAg (both cytoplasmic and membranous) and marked nuclear and focal cytoplasmic immunoreactivity for HBCAg. Cytoplasmic immunoreactivity for HBsAg indicates chronic HBV infection while membranous staining for HBsAg indicates active viral replication. Furthermore, HBCAg immunoreactivity also correlates with degree of viral replication.[12] Hence, the second biopsy indicated that the patient went into a stage of chronic hepatitis B with active HBV replication. The explanation for this could be that the immunosuppressives taken by the patient may have led to an immunotolerant phase resulting in extensive replication of the HBV (replicative phase) and leading on to a chronic carrier state. The immunosuppressive treatment was thus stopped. Six months after the second biopsy, he was detected to have elevated aminotransferases and high viral DNA load (>10^9 IU/ml) on routine testing indicating that the patient had gone into reactivation of hepatitis B following cessation of immunosuppressive. treatment with oral Entecavir 0.5mg/day was hence started with which normalization of aminotransferases was noted on repeat testing two months later.

Gergiadou et al, have reported occult HBV infections with concurrent autoimmune liver disease but the occult HBV infections in his study did not promote the precipitation of AIH. Also, unlike the present case cessation of immunosuppression did not result in HBV replication in any of the cases in his study.[12] However, the literature search did not reveal any case of HBV infection with concurrent AIH or replication of HBV following treatment of AIH in paediatric age group.

Herein, we present a unique case of chronic AIH which was precipitated by acute HBV infection leading on to ACLF which responded to treatment with immunosuppressives but resulted in marked replication of HBV leading on to an immunotolerant phase. Also, cessation of immunosuppressive therapy was the followed by reactivation of Hepatitis B as evidenced by raised aminotransferases and high level of HBV DNA.

References


