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Occult Hepatitis B in Cirrhosis: An Unrevealed Entity

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INTRODUCTION

Chronic liver disease (CLD) is among the most common diseases countered worldwide. According to an Indian registry, 33.9% CLD patients had cirrhosis and almost all cirrhotics (99.4%) had decompensation at the time of diagnosis.[1] Cirrhosis of liver is classically defined by the development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, leading to portal hypertension and end stage liver disease. The decompensation of underlying cirrhosis occurs with onset of variceal bleed and development of ascites with one year mortality rate being 35- 40% and 15-20% respectively.[2] Among the numerous etiological agents for cirrhosis, excessive alcohol consumption and hepatitis virus infections (Hepatitis B and C) have been the most common causes. In Indian context, alcohol consumption is the most common etiology of cirrhosis (34.3%) while hepatitis B virus infection emerged as the commonest cause for non-cirrhotic CLD (40.8%).[1]

In most of the cases, underlying etiology is found after relevant investigations. However in a subset of patients, no etiology is found despite extensive evaluation of all possible etiological factors. Chronic viral hepatitis B and C (CHB and CHC) are usually diagnosed by conventional serological markers; HBsAg and Anti HCV antibodies respectively. With the expanding knowledge of viral structures of hepatitis B and C and better molecular diagnostic techniques, these serological markers are now better considered as screening tools rather than ruling out CHB and CHC. In this regard, we hereby present a case where initially no etiology was found of underlying cirrhosis. On further evaluation by our group patient turned out to be having Occult Hepatitis B (OBI) infection (marker of CHB infection) and was managed successfully with appropriate antiviral drugs.

CASE DESCRIPTION

63 year old male, farmer by occupation presented with complaints of recurrent episodes of hemetemesis (3 episodes within preceding 4 months). In initial two episodes, he was managed conservatively for which no relevant records were available. Patient was asked to have peptic ulcer disease (PUD) and was given treatment in form of proton pump inhibitors (PPIs) for 2 –3weeks after discharge from the hospital on both occasions. He visited our tertiary care hospital when he had third episode of hemetemesis. Patient was managed as per the protocol for hemetemesis and underwent upper gastrointestinal endoscopy (UGIE) which revealed high grade esophageal varices with portal hypertensive gastropathy (PHG).Subsequently endoscopic variceal band ligation (EVL) was done. Patient was admitted for further evaluation.There was no history of yellowish discoloration of sclera or urine, abdominal distension, blood transfusion, high risk sexual behavior and tattoo formation.

On examination, pallor was present with rest of the general and systemic examination being normal. Peripheral signs of CLD were absent with no hepatosplenomegaly. On biochemical investigations, transaminases and alkaline phosphatase levels were normal. Serum albumin was 3.9 g/dl with INR being 1.3. Ultrasonography showed liver measuring 15 cm with irregular outlines with hypertrophy of left lobe and caudate lobe with portal vein diameter (PVD) being 12 mm at porta, findings consistent with liver cirrhosis with portal hypertension.Color doppler study revealed normal triphasic flow in hepatic veins, thus ruling out any possibility of hepatic outflow venous tract obstruction (HVOTO). Contrast enhanced computed tomography (CECT) showed liver cirrhosis with portal hypertension and multiple collaterals seen at porta, peripancreatic, splenic hilum, perigastric and at gastroesophageal junction with splenomegaly and mild ascites. A diagnosis of liver cirrhosis with portal hypertension was made with these two imaging modalities on background history of hemetemesis. Further, we evaluated patient for the underlying cause of cirrhosis. His viral markers for hepatitis B and C were negative. Autoimmune profile for liver diseases (ANA, Anti LKM1, ASMA, IgG, AMA) turned out to be negative. There was no history of alcohol or any prolonged indigenous medicine intake. Iron studies were normal. Kayser Fleischer rings were negative and serum cerulopalsmin levels were within normal range which negated

the possibility of Wilson's disease. Patient was thin built with a BMI of 19.7 kg/m^2 with no background history of diabetes, his lipid profile showed no evidence of dyslipidemia so possibility of non alcoholic steatohepatitis (NASH) leading on to cirrhosis was unlikely in this case.

After these investigations, we planned for other investigations including total Anti HBc antibodies (Total Anti HBcAb; A marker of previous hepatitis Binfection) and quantitative HCV RNA levels to find out any possibility of occult hepatitis B infection (OBI) and seronegative hepatitis C respectively. The next plan of action was to do the liver biopsy to rule out cryptogenic cirrhosis. However, his total Anti HBcAb turned out to be positive (4.66; n < 1) and HCV RNA levels were undetectable (n < 12 IU/ml). Keeping a high possibility of seropositive occult hepatitis B[3] (total Anti HBsAb positive status with negative HBsAg), we ordered for HBV DNA levels which were higher than normal range (2982 IU/ml; n < 20 IU/ml). Owing to this hidden (or rather unexplored) etiology, patient had cirrhosis of liver and had upper GI bleed due to decompensation of underlying cirrhosis. Patient was subsequently started with tab Tenofovir Disoproxil Fumarate (TDF; 300mg) OD for CHB. After 6 months of therapy he had undetectable HBV DNA reflecting complete virological response.[4] Patient had been on regular follow up with continuation of TDF. He is currently on screening protocol for any evidence of hepatocellular carcinoma with 6 monthly USG abdomen, liver function tests and HBV DNA levels with last HBV DNA levels being undetectable.

DISCUSSION

Cirrhosis of liver carries is associated with marked morbidity and mortality with 46% increase in CLD related mortality in the world between 1980 to 2010, mostly reported from low and low-middle income (LMIC) countries of Asia and Africa.[5] In India, cirrhosis of liver accounts for approximately 2 % of death due to all causes. Treatment of underlying etiology is the sole determining factor to prevent its progression. With the better understanding of pathogenesis of cirrhosis, advancement in molecular biology, investigations and advanced imaging techniques, we often are able to find the etiology of cirrhosis in current scenario.

CHB is one of the major causes of cirrhotic as well as non cirrhotic CLD in India as well as worldwide. The prevalence of CHB in general population in India has been estimated to be between 1.4% and 2.7%.[4] CHB is usually ruled out by the absence of hepatitis B antigen (HBsAg) in serum however there is ample data to suggest that in cirrhosis patients, the evaluation beyond this conventional viral marker has to be done before labeling it cryptogenic or no etiology found. The HBsAg and Anti HCV antibodies have been found to be absent in cirrhotic patients despite having these infections as documented by the presence of HBV DNA and HCV RNA in serum. Since our patient had undetectable HCV RNA levels so CHC was ruled out however positive anti HBcAb lead us to further exploration of this case.

HBsAg can be absent from the serum with detection of HBV DNA in the liver (with or without HBV DNA in serum), termed as OBI.[6] OBI can be seropositive or seronegative depending on the presence or absence of total Anti HBcAb.[3,6] The prevalence of OBI varies from 3.9 % to 60 % in different regions of the world[7,8] with 38% reported from India.[9] The prevalence is higher in countries that are endemic for HBV, in individuals with serologic markers of previous HBV infection, and in those with HIV or HCV infection[10] with more common occurrence in patients with cirrhosis or HCC.[6,11]

The presence of HBV DNA in serum sample further confirmed the diagnosis of CHB infection which lead to cirrhosis in this case. Though we did not go liver biopsy to confirm presence of hepatitis B in hepatocytes but with all other etiological factors ruled out, we labelled patient with cirrhosis of liver secondary to CHB. On institution of specific therapy patient responded well with HBD DNA levels undetectable at 6 months post therapy. With this case, we emphasize the importance of unexplored etiological factors in cirrhosis. The various underlying mechanism behind OBI include mutations in the HBsAg gene that prevent detection with monoclonal antibody assays, persistence of immunoglobulin-bound HBV immune complexes, blockage of HBsAg secretion, or viral interference (e.g., coinfection with HCV).[12]

The mechanism of liver damage due to OBI is attributed to persistence and transcription of HBVcccDNA in hepatocytes and subsequently, production of cytokines, such as TNF-α and interferon-γ which might result in damage to heptocytes .[13, 14] The occurrence of mutations in the X region of HBV may result in reduction in the ability of the transactivation of X protein, which is essential for viral replication, and alsoresult in low HBV DNA replication and undetectable HBsAg in serum.[15] Since we did not do any mutation analysis or biopsy in this case so we are not in a position to comment on the mechanism which lead to absence of HBsAg despite persistence of HBV DNA in serum.

To conclude, we state that the screening beyond the HBsAg and Anti HCV antibodies should be done in all cases of liver cirrhosis before labeling them as cryptogenic cirrhosis/ cause not known. The detection of chronic viral hepatitis and subsequent treatment may retard the progression of cirrhosis and leads to favorable outcome.

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