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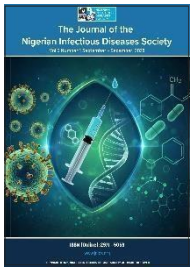

Case Series

Hepatocellular Cancer: An Unpreventable Complication of Chronic Hepatitis B Viral Infection: Case Series

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ABSTRACT

Chronic Hepatitis B virus (HBV) infection is a global public health threat with over 2 billion people been infected with the virus (one out of three people), about 1.5 million are newly infected each year and almost 300 million people chronically infected. An estimated 820,000 people die each year from hepatitis B related complications such as liver cancer.

It was observed that despite treatment with potent Nuleo(s)tide Analogue and Pegylated Interferon-alpha as recommended by various guidelines, chronically infected patients still developed the major complication of Hepatocellular cancer.

In this case series, we were able to obtain comprehensive record of four cases managed at private facility in Kano, Nigeria, who without significant risk factors for HCC other than CHB and developed HCC despite aggressive management with potent NAs and/or PEGINF-α. The implication of this is that, are our guidelines sufficient to prevent this scourge of HCC or there is need for a better curative measure for the management of CHB.

Keywords: Chronic Hepatitis B virus infection, Hepatocellular Cancer, HBV DNA viral load, Nucleo(s)tides Analagues, Pegylated Interferon-alpha

INTRODUCTION

Chronic Hepatitis B Viral Infection is a preventable disease through routine vaccination and treatment of infected mother during pregnancy. Also, sero-conversion had been reported occasionally either spontaneously or on treatment. However, a large number of infected patients would continue to express evidence of the infection even with treatment.

The world prevalence of HBV infection is estimated to be around 2 billion, 240 million people expressed the evidence of chronic carriers of HBV[1]. The South-east Asia, China, Sub-Sahara Africa and Amazon basin accounted for 75% of chronic carrier state[2] and 15-40% of the CHB would develop Cirrhosis or Hepatocellular cancer[3].

Several studies have established that there is a specific and consistent causal relationship between CHB infection and HCC[4,5]. In patients with chronic persistent infection, the risk of HCC was 100 times higher than in non-infected individuals[4]. The global distribution of HCC closely related to the geographical prevalence of CHB, estimated 400 million cases worldwide with highest rates in south-east Asia and Sub-Sahara Africa (incidence of >50/100,000 population[6]).

All guidelines[7,8,9,10] adopted treatment options for active CHB as preventive measures for Liver cirrhosis and/or HCC. Currently, there are two main treatment options for CHB patients; treatment with a Nucleo(s)tide analogues (NAs) or with Polyethylene glycol (PEG)ylated Interferon-alpha (PegIFN-α). The NAs that have been approved include Lamivudine (LAM), Adefovir dipivoxil (ADV), Entacavir (ETV), Telbivudine (TBV), Tenofovir disoproxil fumarate (TDF) and Tenofovir Alafenamide (TAF) as a monotherapy[7,11]. However, despite all the concerted efforts by several groups (AASLD[7], APASL[8], EASL[9], and SOGHIN[10]) at formulated a workable guidelines for treatment of HBV infection, HCC frequently occurred in CHB infected patients. Hepatocellular Cancer is currently the main concern for diagnosed CHB patients and had been shown to have develop even in patient who have been effectively treated [12,13].

Here we report four cases of Chronic Active stage of HBV infection managed in a private facility in Kano, Nigeria who developed HCC close monitoring and management.

Case 1:

Mr. CBA is 62-year-old retired Custom officer who was diagnosed to Chronic HBV infection during pre-employment medical screening about 35 years ago. He had been on regular follow-up until 15 years later when he started experiencing recurrent tongue and mouth ulcers and was offered treatment with Lamivudine 150mg daily. After about 10 years on Lamivudine, the HBV-DNA viral load was 1,526 iu/mls. Attempt were made to use a weekly 180µg Pegylated Interferon injections, however he could not tolerated the side effects of the Interferon and was stopped after 2 months therapy. The Lamivudine was then changed to Entacavir 1mg daily with remarkable improvement, repeated laboratory parameters including HBV-DNA levels were better. He claimed to have adhered strictly to his medication but was not regular on clinic visits due to the nature of his job.

Two years ago, following his retirement, he started experiencing progressive weight loss, abdominal swelling, passage of malaena stool and significant body weakness.

Examination revealed a middle-aged man, chronically ill-looking, paled, aniteric, but significant peripheral stigmata of CLD and pitting pedal oedema. The abdomen revealed a hard, nodular liver, span of 20cm and moderate ascites. The cardiovascular, respiratory and central nervous systems were essentially normal. His abdominal CT scan shows a moderately enlarged nodular liver with heterogenous parenchymal density, the conclusion was CLD with likely malignant transformation. Abdominal MRI showed the Liver to be enlarged measuring 25.4cm in its craniocaudal span with heterogeneous parenchymal signal intensity and nodular outline. There are multiple ill-define T1/T2W hyper-intense masses seen scattered predominantly in the right lobe of the liver and few seen in the left lobe. MR finding are those of multifocal nodular non-enhancing lesion suggestive of PLCC.

He was started on Sorafenib 200mg bd but died shortly from Hepatic Encephalopathy.

Case 2:

Mr. SM, a 48 year old Civil Engineer who is a type 2 Diabetes Mellitus patient, was diagnosed to have Chronic HBV infection during routine medical check-up in the year 2016.

The initial laboratory results showed markedly high HBV-DNA viral load 474,500 iu/ml, elevated Aminotransferases and HBeAg negative. He was initially commenced on 180µg weekly Pegylated Interferon-alpha (Pegasys®) subcutaneous injections for a years and there was significate improvement on the laboratory parameters.

However, 1 year after the completion of Interferon therapy, the follow-up HBV-DNA viral load result was noticed to be high 19,071 iu/ml from the previously post-treatment undetectable level. He was offered to start Tenofovir Alafenamide (Vemlidy®) 25mg daily. Two years into the treatment with TAF, he started experiencing vague right sided upper abdominal pain. The pain is aggravated by deep inspiration, no cough or difficulty in breathing. No jaundice, body swelling or bleeding from any orifices. Examination revealed a middle aged, calm, not pale, aniteric, acyanosed, no significant peripheral stigmata of CLD and no pedal oedema. Abdomen was full and soft, no area of tenderness, Liver span of 10cm not palpably enlarged and no Ascites.

Serial investigation results; Abdominal USS (28/07/20) shows normal in size however, the liver parenchyma appears coarse with accentuated brightness of portal vein radical walls suggestive of Acute Hepatitis. Abdominal USS (11/02/21) there is coarse echo texture of the liver with decreased echogenicity in-keeping with Macronodular cirrhosis. Abdominal USS (22/08/21) the Liver have coarsened parenchymal echo-texture, no definite focal lesion. Abdominal USS (25/06/22) the Liver shows uniform parenchymal echo-pattern and regular outline however, there is a small oval-shaped well outlined echogenic lesions in segment II measuring 0.9 x 1.77cm in size. Abdominal CT scan shows that the Liver have an area of abnormal density in VI and VIII. The lesion has an ill-defined iso- and hypodensity with peripheral enhancement of the mass in the arterial phase and complete washout of contrast in the venous phase. The remaining part of the liver parenchyma appears within normal limits. The CT findings are suggestive of PLCC. Image guided Liver biopsy histology reveals that the features are in keeping with early well differentiated Hepatocellular carcinoma against background liver cirrhosis.

He was referred to India for hepatic resection however the PET scan shows severe Portal vein thrombosis. He was then offered immunotherapy with Atezolizumab 1200mg/ Bevacizumab 1000mg and was only had two sessions before his demised.

Case 3:

Mr. JB is 47 years USAID staff that was first seen in August 2020 with complains of recurrent belching, Abdominal bloating and epigastric pain. He was recently diagnosed to have Chronic HBV infection with markedly elevated HBV-DNA viral load >1,000,000 iu/mls, HBeAg negative and was immediately commenced on Tenofovir Alafenamide (Vemlidy®) 25mg daily since October, 2020 with significant improvement in the laboratory parameters.

Serial HBV-DNA viral loads were as follows: in October 2020 it was <20iu/mls, in April, 2021 it was slightly elevated 783iu/mls, in October, 2021 it became undetectable again <15iu/mls, so also in June 2022 <15iu/mls and similarly in March, 2023 <1iu/mls.

However, about a three month ago, he started experiencing frequent micturition no associated dysuria or fever and no osmotic symptoms. The attending Physician requested for Abdominal ultrasound scan which incidentally reveals an enlarged Liver with coarsened parenchymal echotexture and a large well-defined heterogeneously hypoechoic rounded mass lesion measuring 86x76 mm, likely PLCC to rule out Lymphoma/Leukemia and keep-in-view the possibility of secondary Liver metastasis. Triple phase Abdominal CT scan shows that there are multiple heterogeneously enhancing hypo-to- iso-dense mass lesions of varying size and shape. They showed complete washout, largest measuring 45.3x43.5 mm, likely diagnosis was Hepatocellular carcinoma.

Alfa Feto-Protein was >400ng/mls.

He was referred to India for possible Hepatic resection +/- Trans-Arterial Chemo-Embolization (TACE). However, the PET scan shows Portal vein thrombosis and Pulmonary Artery metastasis. He had four sessions of immunotherapy with Atezolizumab 1200mg/ Bevacizumab 1000mg before his demise.

Case 4:

Mr. IJ Businessman was diagnosed to have chronic Hepatitis B viral Infection in 2003 during screening for blood donation and had been on regular clinic follow-up and routine laboratory investigations for nearly 20 years. In 2022 the investigation results were noted to be deranged with HBV-DNA viral load of 9,142 iu/mls, HBeAg negative, ALT was elevated, AFP was 28.8 ng/mls and Abdominal USS shows Solitary Hepatic mass ?Haemagioma. Abdominal CT scan (Triple Phase) confirm the mass to be Hepatic Haemagioma.

No history of jaundice, body swelling or bleeding from any orifices. He does not smoke cigarette nor ingest alcohol. Not a known HTN/DM. Physical examinations were essentially normal. He was commenced on Pegylated Interferon 2-alfa (Pegasys®) 180µg weekly for a year with significant improvement.

Serial investigation results over the past 3 years were normal; HBV-DNA viral load (25/09/22) was 9,142.8 iu/mls. Abdominal USS (20/08/22), the liver show a solitary mass occupying segment VIII, hyperechoic measuring 85x81 mm in size, likely Hepatic Haemagioma. Also, Abdominal CT Scan (23/08/22) shows that there is fairly oval shaped heterogeneously enhanced hypodense mass (HU = 17-48) in segment VIII of the liver, the findings are those of Hepatic Haemagioma. HBV-DNA viral load on (28/02/23) was 53 iu/mls. Abdominal USS (01/03/23) still shows Hepatic Haemagioma. HBD-DNA viral load on (01/05/23) was 75.7 iu/mls and similarly, HBD-DNA viral load on (14/11/23) was 5.6 iu/mls.

However, after a year post Interferon therapy, the HBV-DNA viral load result was found to have increased to 2000 iu/mls and Abdominal USS shows the usual Hepatic Haemagioma to rule-out HCC. Triple Phase Abdominal CT Scan done showed that there are multiple fairly oval shaped hypodense lesion (6-42 HU) seen within the liver parenchyma. The largest is seen in segment V measuring 8.8x9.8x9.8 cm in dimension. The conclusion was Hepatocellular carcinoma.

Abdominal CT scan done in Egypt hospital shows the liver to be mildly enlarged measuring 17cm with evidence of right hepatic lobe infiltrative process evidence by a large well-defined heterogeneously enhancing focal lesion occupying segment VIII and V measuring 8x7x9 cm as well as an adjacent ill-defined area occupying segment VI showing relative washout in portovenous and delayed phase. Another smaller adjacent lesion showing heterogeneous enhancement is seen at subcapsular region of segment VII measuring 2.5x2.3 cm. Another small non-enhancing focal lesion is seen at segment II measuring 6.6x4.3 mm. There is thickened peritoneal reflection overlying the right hepatic lobe with subsequent scalloping of the right hepatic border. The right portal vein and its branches as well as the right hepatic vein are not visualized likely infiltrated by the aforementioned lesions. Conclusion is that of Right hepatic lobe infiltrative lesions likely HCC.

DISCUSSION

Hepatocellular Cancer (HCC) is commonest complication of CHB with high morbidity and mortality, annually 500,000 to 1.2 million people die of CHB infection worldwide[14,15].

The four patients presented in this study developed HCC despite strictly adherence to the treatment guidelines. Contrary to the earlier believes that long-term treatment with Entacavir (ETV) or Tenofovir (TDF) monotherapy had shown to halt the progression of liver diseases and can also results in a significant improvement of the histological necro-inflammation and fibrosis with regression of established cirrhosis[16].

Also, the risk of development of HCC has been higher in patients with one or more factors that related to the host like the presence of cirrhosis, chronic necro-inflammation, older age, male, sex, African-origin, alcohol abuse, co-infection with other hepatitis viruses/HIV, Diabetes Mellitus/metabolic syndrome, active smoking, positive family history and/or to HBV properties (high viral load and/or HBsAg levels, HBV genotype C>B, specific mutations[12]. In our reported cases, very few of the numerated factors were observed, apart from been of African-origin and male sex, all the patients were of relatively younger age group, only case 2 had DM and none of them ever smoke cigarette, ingest alcohol and no family history of HCC. Additionally we were able to achieve and sustained undetectable viral load in all the patients. However, study had shown that, these factors are only more important in an untreated CHB patient[13].

In a prospective study in Taiwan[17], it was shown that Relative Risk of HCC among men who were positive for both HBsAg and HBeAg (RR = 60.2) were much higher than that among men who were positive for HBsAg alone. Furthermore, HBV DNA was identified as the most important predictor of the development of HCC in HBsAg positive patients and it was concluded in the studies that efforts at eradication or reduces the viral load may decrease the risk of HCC[18,19]. However, in this study all the patients were HBeAg negative and also HBV DNA consistently suppressed.

It is important to emphasize that the presence of the HB virus alone is enough to cause HCC and CHB infection is the second carcinogen after Tobacco according to the WHO. The possession of HBx gene by HBV has been shown to have pleiotrophic function such as regulation of transcription and oncogenic activity which is largely responsible for the carcinogenic property of the virus[20].

Additionally, the Circularly-Closed-Covalent DNA (cccDNA) is the transcription template for HBV mRNA21, the cccDNA is incorporated into the host DNA and converted it to RNA which further reproduced more viral DNA particles thereby serving as an Oncogenic Molecules. This unique property makes it difficult to design a curable molecule to the infection and its associated oncogenicity[20,21].

It is necessary therefore, for a more robust guidelines aiming at preventing the complication of CHB- related Liver Cirrhosis and/or Hepatocellular carcinoma especially for the African patients because of their peculiarity.

Additionally, curative medications as existed for the treatment of Chronic Hepatitis C viral infection as envisaged by a group of workers, the International Coalition to Eliminate HBV (ICE-HBV) with the various studies designs at eradication of CHB in the next 5 years [22] were necessary to halt the suffering both clinical and emotional of the patient with CHB infection.

SUMMARY

CHB infection is dreaded disease with over 2 billion individual infected worldwide and associated significant morbidity and mortality. Several drugs had been approved for the treatment of the infection and every region of the world has a guideline to assist clinician in the management of the infection. However, HCC complication frequently still exists in these set of patients despite intensive measures and adherence to the guideline, this is as shown in our case series. It is important therefore, to aim for a curative drug as existed for chronic hepatitis C viral infection.

Declarations

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