Case Report

Diagnostic Value of Alpha-Fetoprotein for Early Hepatocellular Carcinoma Diagnosis in Cirrhotic HBV Patient Successfully Treated with Nucleos(T)ide Analogues — A Case Report

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Abstract

Despite sustained viral suppression, hepatocellular carcinoma (HCC) can still develop in cirrhotic patients treated with entecavir (ETV) or tenofovir (TDF). Because early HCC diagnosis increases the applicability of curative therapies, the identification and close surveillance of high-risk patients for HCC development is of great importance. Ultrasound examination of the hepatic parenchyma (USG) is considered the most sensitive screening tool for high-risk patients, while the diagnostic role of serum alpha-fetoprotein (AFP) is controversial.

Herein, we report a case of a 43 year-old Caucasian man with HBV-HDV related cirrhosis, treated with ETV monotherapy. During antiviral therapy, HCC surveillance was performed semestrally using USG and serial AFP measurements. After 3 years of sustained viral suppression, the patient showed a slight increase in AFP levels with absence of neoplastic lesions detected by USG. A further increase of AFP levels was demonstrated arousing suspicion of HCC development, confirmed by magnetic resonance imaging. The timely HCC diagnosis made the option of liver transplantation possible, with a significant impact on patient prognosis.

In conclusion, this case emphasizes the diagnostic value of AFP for early HCC diagnosis in high risk patients treated with nucleos(t)ide analogues, suggesting its utility in combination with USG for HCC surveillance.

ABBREVIATIONS

HBV: Hepatitis B Virus; NA: Nucleos(T)ide Analogue; CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; AFP: Alpha-Fetoprotein; ETV: Entecavir; TDF: Tenofovir Disoproxil Fumarate; USG: Ultrasound Examination of the Hepatic Parenchyma; EGD: Esophagogastroduodenoscopy; RMI: Contrast-Enhanced Magnetic Resonance Imaging

INTRODUCTION

Chronic hepatitis B virus (HBV) infection affects over 250 million people worldwide and remains one of the leading causes of cirrhosis, liver failure and hepatocellular carcinoma (HCC). Currently, entecavir (ETV) and tenofovir disoproxil fumarate (TDF), third generation oral nucleos(t)ide analogues (NA) recommended by all international guidelines as first-line monotherapy, suppress HBV replication in almost all compliant patients with chronic hepatitis B (CHB) [1-3]. The long-term inhibition of HBV replication translates into several clinical benefits including the prevention of progression to cirrhosis and clinical decompensation, the improvement of portal hypertension in compensated cirrhotic patients, the reversal of hepatic decompensation, the reduced need for liver transplantation and overall, an improved survival. However, despite virologic suppression, the risk of HCC development can be reduced but not eliminated [4]. A recent multicentre retrospective study in CHB Caucasian patients indicated that HCC may still develop under effective long-term ETV or TDF therapy [5]. Therefore, in virologically suppressed patients, HCC surveillance remains necessary in order to improve patient outcome by increasing early HCC detection and the possibility of curative treatment.

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[2,6]. Alpha-fetoprotein (AFP), a serum biomarker widely used in clinical practice for early HCC diagnosis, has a controversial role as a diagnostic tool because of its low sensitivity and specificity, and limited accuracy for detecting small HCC nodules [7,8]. However, recent studies have shown that AFP may be useful for monitoring the response to HCC therapy and have recommended this test for post-treatment follow-up, in fact, a decline in AFP concentration is thought to indicate a favourable response and an improved outcome [9]. As yet, there is a lack of information on the behaviour of AFP in virologically suppressed CHB patients, and it remains unclear if AFP could be a useful test for HCC surveillance.

Herein, we report and discuss the vital and decisive role of AFP monitoring for early HCC diagnosis in an HBV cirrhotic patient who developed HCC during long-term effective ETV treatment.

CASE REPORT

A 43-year-old Caucasian man was tested HBsAg-positive in 1989 during viral hepatitis screening performed due to ALT elevation. At first observation, the patient was positive for anti-HBe, HBV DNA, IgG and IgM anti-HDV. A liver biopsy demonstrated a METAVIR F4 fibrosis score; an esophagogastroduodenoscopy (EGD) indicated the absence of esophageal varices. An HBV/HDV-related cirrhosis was diagnosed and a 12-month course of standard IFN (lymphoblastoid 6.000.000 x 3 weekly for 12 months) was performed without virological and biochemical response.

From 1991 to 2005, the patient was subjected only to laboratory tests showing a fluctuating ALT and HBV DNA levels and a persistent positivity for IgM anti-HDV. In 2006, a second Peg-IFNa2a treatment was initiated. During treatment, HBV DNA became negative, but ALT levels remained high, and therefore after 8 months Peg-IFN was discontinued. In May 2009, due to serum HBV DNA reappearance, ETV monotherapy was administered, thus achieving a rapid virological and biochemical response. During therapy, the patient underwent HCC surveillance with USG and AFP measurement every six months. The AFP levels were normal until March 2012, when a slight increase was noted, but no lesions were detected by USG. In the following 4 weeks, a further increase of AFP levels was demonstrated arousing suspicion of HCC development (Table 1). A contrast-enhanced magnetic resonance imaging (RMI) was performed, showing three hepatic nodules with arterial uptake followed by washout (one of 2.5 cm ½ in VII segment, and two less than 1cm in the VIII-III segments), both nodules were specific for HCC. The presence of HCC nodules was also confirmed by contrast-enhanced computed tomography. Serum AFP levels continued to increase and, in June 2012, the patient was referred to a Liver Transplant Center and successfully transplanted in October 2012.

DISCUSSION

The case herein underlines the decisive role of AFP for early HCC diagnosis in a cirrhotic patient with sustained virological suppression during ETV therapy.

Despite the dramatic improvement of CHB therapy with third generation NAs, HCC development remains a major complication and a key challenge for CHB patient management. As early HCC diagnosis increases the applicability of curative therapies, the timely identification and close surveillance of high-risk patients for HCC is of great importance. Recently, an HCC risk score (PAGE-B) has been developed in CHB Caucasian patients being treated with a 5-year ETV or TDF therapy. The score, based on gender, baseline patient age and platelet count, may assist clinicians to stratify the HCC risk and to determine the target population for surveillance [10]. An important issue related to the surveillance program is which tests should be used and the frequency of screening. In cirrhotic patients, EASL and AASLD Guidelines recommend HCC surveillance with USG every 6 months [1,2]. However, the case presented shows that a surveillance program with USG alone can fail to diagnose small lesions, leading to a HCC diagnosis too late for a curative treatment. On the contrary, in our patient, AFP monitoring in combination with USG, as recommended by APASL guidelines [3], allowed us to suspect HCC development even in absence of lesions on USG screening. In fact, the slight increase in AFP levels, led us to promptly perform an MRI, thus allowing early HCC detection. The timely diagnosis of HCC made the option of liver transplantation possible, with a significant impact on patient prognosis. These data suggest that, contrary to that observed in untreated cirrhotic patients, in whom elevated AFP levels are seen in absence of neoplastic transformation (low specificity), AFP returns to be a sensitive marker of HCC in cirrhotic patients with sustained HBV suppression and normal ALT levels treated with NAs.

In conclusion, the case presented emphasizes the diagnostic value of AFP for early diagnosis of HCC in high-risk patients, even in absence of neoplastic lesions at USG, thus permitting curative treatments and improving prognosis. If further studies on a larger number of NA-treated patients confirm these data, USG and AFP every 6 months should be recommended as an important screening tool for high-risk patients.

ACKNOWLEDGMENTS

The authors are grateful to Ms. Paulene Butts for her assistance in the preparation of the manuscript.

REFERENCES

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