

Close Association of AFP Level with HBV-DNA Increase Caused by Lamivudine And Adefovir Resistance

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ÖZET

Lamivudin ve adefovir direncine bağlı HBV DNA artışının AFP seviyesiyile ilişkisi

Serum alfa fetoprotein (AFP) seviyelerindeki belirgin yükselme hepatosellüler karsinoma tanısında oldukça anlamlı olup ileri araştırmayı gerektirir. Lamivudin ve adefovir direnci sonrası viral atak ve akut hepatit alevlenmesi ile serum AFP seviyelerinde belirgin artış gösteren kronik hepatit B vakasını sunacağız. Hasta adefovir ve entecavir tedavisi sonrası belirgin bir şekilde düzeldi.

Anahtar kelimeler: Alfa fetoprotein, kronik hepatit B, lamivudin direnci, adefovir direnci, entecavir.

ABSTRACT

Close association of AFP level with HBV-DNA increase caused by lamivudine and adefovir resistance

Marked elevations in serum alpha fetoprotein (AFP) levels are highly suspicious for hepatocellular carcinoma and should prompt an extensive diagnosis. We report a case of chronic hepatitis B where episodes of marked elevations in serum AFP levels occurred, after viral breakthrough and acute exacerbation of hepatitis following development of lamivudine and adefovir resistance. The patient had a prompt improvement after adefovir and entecavir treatment, respectively.

Key words: Alpha fetoprotein, chronic hepatitis B, lamivudine resistance, adefovir resistance, entecavir.

Bakırköy Tıp Dergisi 2010;6:39-41

INTRODUCTION

Alpha fetoprotein (AFP) has a role for establishing a non-invasive diagnosis of hepatocellular carcinoma (HCC) when markedly elevated in patients with a detectable liver mass (1). Thus, serum AFP levels more than 200 (1) and 400 ng/ml (2) prompt a physician to identify any underlying HCC. However, there are also non-malignant causes of elevated serum AFP levels in some patients, such as cirrhosis and hepatitis (3,4,5). In this report, we presented a patient with chronic hepatitis B who experienced episodes of marked elevations in serum AFP levels occurring concurrently with the resistance to lamivudine and adefovir.

CASE REPORT

A 59-year-old woman with chronic HBV infection was referred for initial evaluation. She had nonspecific symptoms including fatigue and abdominal discomfort, and there were no signs of chronic liver disease on physical examination. Initial laboratory tests to assess liver disease were as follows: albumin 3.9 g/dl; bilirubin 0.9 mg/dL; prothrombin time 13 seconds; platelets 137.000/mm³; alkaline phosphatase 256 U/L; alanine aminotransferase (ALT) 27 U/L; and aspartate aminotransferase (AST) 37 U/L. Hepatitis B surface antigen (HBsAg) and antibody to hepatitis B e antigen (anti-HBe) were positive. The HBV DNA level was 4.2x10⁵ copies/mL by polymerase chain reaction analysis (lower limit of detection, 1x10³ copies/mL). Her alpha fetoprotein (AFP) level was 37 ng/mL (normal range, 0-7 ng/mL). Imaging studies, including abdominal sonography, and magnetic resonance imaging, showed no liver mass. Serial serum analysis demonstrated a gradual increase of AFP levels to a peak level of 131 ng/mL. Then, her AFP levels

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Geliş tarihi / Date of receipt: 11 Mayıs 2009 / May 11, 2009

Kabul tarihi / Date of acceptance: 1 Eylül 2009 / September 1, 2009

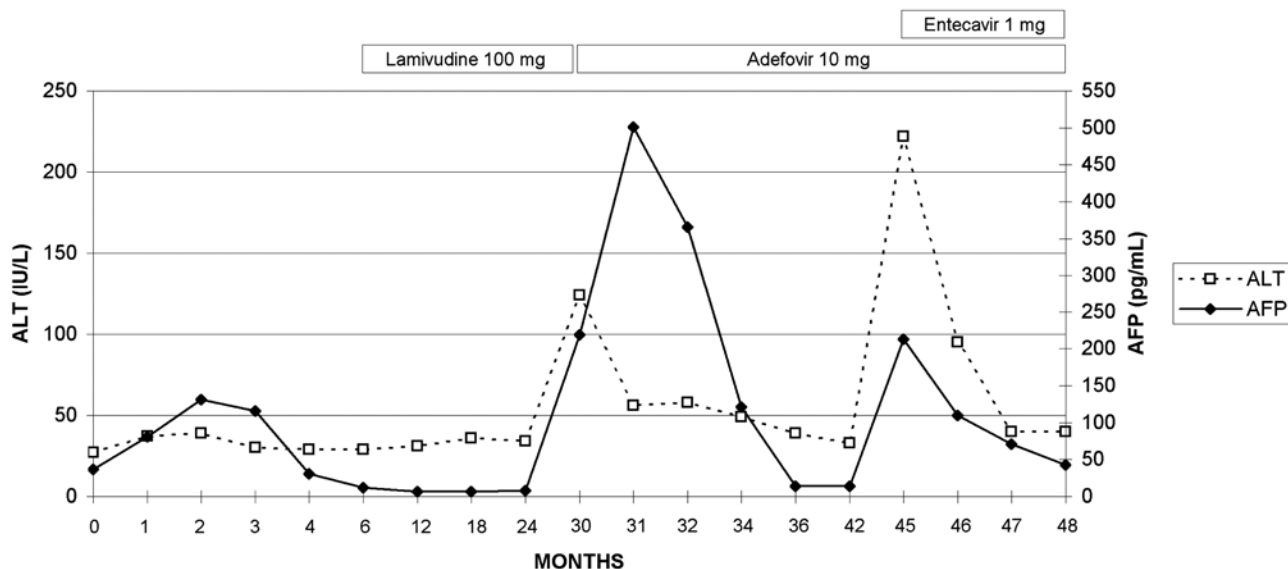


Figure 1: Clinical course of the patient showing acute exacerbation of hepatitis B following lamivudine and adefovir resistance and episodes of AFP elevations

decreased to previous levels, and this episode without increase in aminotransferase levels lasted for 4 months (Figure 1).

Although her aminotransferase levels were normal, liver biopsy was performed because of HBeAg negative chronic hepatitis with persistent viral replication that led us to suspect an advanced liver disease. Liver biopsy revealed histological activity index score (HAI) of 7/18 and fibrosis grade 4/6. Treatment with lamivudine (100 mg once daily) was started at month 6. At the follow up, six months after initiation of lamivudine therapy, HBV DNA level became undetectable (lower limit of detection, 2×10^2 copies/mL) and AFP level further decreased to normal levels. After 24 months of lamivudine therapy, ALT and AFP levels raised to 124 IU/L and 219 ng/mL, respectively. Viral breakthrough was detected by increase in HBV DNA level of 8.6×10^6 copies/mL, which was confirmed to be due to YVDD mutants. Ultrasonography and computed tomography for detailed examination failed to detect the presence of a liver mass. She was switched from lamivudine to adefovir therapy. The peak AFP level during the second episode was 501 ng/ml. Six months after initiation of adefovir therapy, her ALT and AFP levels decreased to 33 IU/L and 14 ng/mL, respectively (Figure 1).

During the period of follow-up, 45 months after initial evaluation and 15 months after initiation of adefovir therapy, she had another episode of AFP elevation

with hepatitis flare and virological breakthrough. In this episode, her AFP level was 213 ng/mL, with an ALT level of 222 IU/L and HBV DNA concentration of 3×10^6 copies/mL. Virologic resistance to adefovir was detected in association with polymerase mutation A181T/V. No liver mass was identified on sonography. Entecavir 1 mg was prescribed for the patient as add-on therapy. After 3 months, her ALT and AFP levels decreased to 40 IU/L and 43 ng/mL, respectively (Figure 1).

DISCUSSION

Alpha fetoprotein can be particularly useful in early identification of HCC. But, the sensitivity and the specificity vary from 25% to 65% and 79% to 95%, respectively (6). Thus, the primary diagnostic value of serum AFP for the detection of HCC is limited because serum AFP is sometimes elevated in patients with non-malignant liver diseases (3,4,5). In a cohort of 166 patients with chronic hepatitis B, 29 episodes of elevations in serum AFP levels identified, mainly due to exacerbation of underlying hepatitis (4). These exacerbations were associated HbeAg seroconversion or unknown causes. But, in some patients with AFP elevation, there was no acute exacerbation explaining the episode (4).

In the present case, the patient had three episodes of marked elevations of serum AFP levels. No explanation was found for the first episode without increase in

serum aminotransferases, but the last two episodes were obviously associated with lamivudine and adefovir resistance, respectively. These two episodes may be explained by viral breakthrough due to drug resistance, and acute exacerbation of hepatitis B. Acute exacerbations of hepatitis are accompanied by some degree of liver regeneration, and AFP expression can resume during regeneration (7). In addition to liver regeneration after acute exacerbation of underlying hepatitis, we do not know whether HBV drug resistance is associated with elevation in serum AFP levels. In studies of HCC, it was shown that the expression of AFP is affected by ethnicity (8), etiology of liver disease (9), presence of cirrhosis (10) and p53 mutation (9). Also, genetic mutations in the basal core promoter and precore regions of the HBV genome were found to be predictive for HCC development (11). Therefore, the role of mutations of drug resistant chronic

hepatitis B in the pathogenesis of severe liver disease and HCC, and their potential interaction in AFP elevation remain to be explained.

The clinically important point to emphasize is that the elevations of serum AFP levels were transient in the patient. We know that progressive elevation of AFP in patients with chronic liver disease may indicate progression of HCC (12). In a previous report, it was observed that markedly elevated AFP levels of >1,000 ng/mL in three patients decreased to the normal range after initiation of lamivudine treatment. In the present case, similar reduction of serum AFP levels was observed after adefovir and entacavir treatment.

In conclusion, serum AFP levels are not only associated with cirrhosis and HCC, but may increase in parallel with HBV-DNA levels following drug resistance and act as a marker for viral replication.

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