Elevated Alpha Fetoprotein, No Hepatocellular Carcinoma

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Alpha fetoprotein is a fetal specific glycoprotein which falls rapidly after birth. High level of alpha fetoprotein is suspicious of hepatocellular carcinoma but may be elevated in chronic viral hepatitis. A 35-year-old presented to us with jaundice for 7 days. He had chronic hepatitis B infection for last 12 months and was taking medicines irregularly for same. He had high alpha fetoprotein levels (740.9 ng/ml) without evidence of hepatocellular carcinoma which reduced with antiviral therapy. Such elevation can be explained due to hepatic inflammation and viral replication. (J CLIN EXP HEPATOL 2013;3:162–164)

Alpha fetoprotein (AFP) is a fetal specific glycoprotein produced primarily by the fetal liver. Serum AFP level falls after birth and its synthesis is suppressed in adult life. Serum AFP can become elevated in some disease states particularly hepatocellular carcinoma (HCC), but may still be non-specific finding in patients with chronic viral hepatitis. We present a case with elevated AFP without evidence of a tumor. Serum AFP levels decreased in response to antiviral therapy.

CASE REPORT

A 35-year-old South African origin male had chronic hepatitis B infection diagnosed for last 12 months following an episode of jaundice. He was started on combination tablet of lamivudine 300 mg and tenofovir 300 mg once a day in South Africa. He was not compliant with these drugs and had stopped the tablet for last 1 month. At the time of admission to St John's Medical College, Bengaluru, he presented to us with jaundice, nausea, anorexia and loss of appetite for last 7 days. There was no history of abdominal pain, itching or clay colored stools. There was no history of any hepatotoxic drug, ethanol or herbs consumption and exposures to toxins. Physical examination revealed scleral icterus, chronically ill appearing man

with hepatomegaly and no ascites or asterixis. There was no Kayser–Fleischer ring, pedal edema, spider-nevi, gynecostasia, testicular atrophy and caput medusa.

Laboratory evaluations revealed total hyperbilirubinemia (11.84 mg/dl) with conjugated hyperbilirubinemia (8.69 mg/dl), aspartate aminotransferase (AST) 2163 U/L (normal 15–37 U/L), alanine aminotransferase (ALT) 2760 U/L (normal 30–65 U/L), alkaline phosphatase (ALP) 174 U/L (normal 50–136 U/L), gamma glutamyl transferase (GGT) 181 U/L (normal 15–85 U/L), albumin 3.6 g/dl (normal 3.4–5.0 g/dl). Prothrombin time was elevated by 7 s with international normalized ratio of 1.6. Ultrasonography of abdomen showed enlarged liver (15 cm) with normal contour, borders and no focal lesions, normal portal vein and spleen with no free fluid. Tests for other hepatotropic viruses like IgM anti-hepatitis A virus, IgM anti-hepatitis E virus, anti-hepatitis C antibodies, anti-hepatitis delta virus were negative. Hepatitis B surface Ag was positive with negative hepatitis B envelope Ag and IgM anti-hepatitis B core. Antinuclear antibody (ANA), anti-liver kidney microsomal antibody (anti-LKM-1), anti-smooth muscle antibody (ASMA) were negative. Serum ceruloplasmin was 24 mg/dl (normal 18–45 mg/dl). Gastroscopy done showed no evidence of portal hypertension. Hepatitis B virus DNA was 9911 IU/ml (real time polymerase chain reaction method). He was further evaluated for acute on chronic liver disease etiology with AFP, which came out to be 740.9 ng/ml (normal 0.5–7.0 ng/ml). The triple phase contrast enhanced CT scan of abdomen (Figures 1 and 2) revealed no focal lesions in liver, portal vein thrombosis or ascites. A liver biopsy could not be carried out on account of the patient's adamant refusal. He was diagnosed to have severe flare of hepatitis B virus infection due to discontinuation of therapy. He gradually felt better with an improved appetite.

He was later discharged with same therapy which he was taking prior after counseling regarding compliance. By 4 weeks into treatment, his improved liver biochemical tests showed total bilirubin level 1.8 mg/dl (conjugated bilirubin

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Abbreviations: AFP: alpha fetoprotein; HCC: hepatocellular carcinoma; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase; ANA: antinuclear antibody; anti-LKM-1: anti-liver kidney microsomal antibody; ASMA: anti-smooth muscle antibody; HBeAg: hepatitis B virus e antigen; LCA: lens culinaris agglutinin

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Figure 1 Contrast enhanced CT scan abdomen showing normal liver.

0.9 mg/dl), AST 35 U/L, ALT 56 U/L, ALP 115 U/L, GGT 45 U/L, total protein 6.9 g/dl, albumin 3.8 g/dl and normal prothrombin time. His AFP levels reduced to 185 ng/ml. His repeat ultrasound of liver showed no liver lesion. The dramatic decrease in the AFP levels is not likely to be a spontaneous event, but possibly due to suppression of viral replication and hepatic inflammatory activities by antiviral drugs.

DISCUSSION

Hepatocellular carcinoma (HCC) develops during natural history of cirrhosis, the risk is higher in patients with viral hepatitis. HCC develops in one-third of cirrhotic during their lifetime.¹ Long-term follow-up studies have revealed that HCC develops in approximately 1–8% per year of patients with cirrhosis with 2% in HBV-infected and 3–8% in HCV infected cirrhotic patients. Key predictors of

Figure 2 Contrast enhanced CT scan abdomen showing normal liver.

HCC development in patients with chronic hepatitis B infection are hepatitis B virus e antigen (HBeAg) seropositivity, high viral load, and genotype C with hepatitis B viral load correlating with risk of progression to cirrhosis.² HCC surveillance includes imaging and serological tests. Imaging tests include ultrasonography or triple phase computed tomography. A serological test that is commonly performed includes AFP.

AFP is a glycoprotein primarily produced by the fetal yolk sac, liver and intestine. Its production is almost totally suppressed after birth with concentration decreasing to <10 ng/ml. Low grade elevation of AFP is seen in benign liver disease including acute and chronic hepatitis and cirrhosis, but values above 200 ng/ml are used as a surrogate marker for HCC.² When used for diagnosis of HCC, serum AFP values higher than 20 ng/ml showed sensitivity ranging from 41% to 65%, specificity ranging from 80% to 94%, positive likelihood ratio ranged from 3.1 to 6.8 and negative likelihood ratios ranged from 0.4 to 0.6.³ The positive predictive values for diagnosis of HCC reached 100% in the non-viral diseases with serum AFP levels of 100 ng/ml, while in the viral diseases it was 100% with levels greater than 400 ng/ml⁴ and hence values greater than 400 ng/ml are considered diagnostic of HCC.⁵

AFP can be divided into different glycoforms depending on their binding capacity to lectin lens culinaris agglutinin (LCA). The different glycoforms of AFP include AFP-L1, AFP-L2 and AFP-L3. AFP-L1 is the non-LCA-bound fraction and is the major glycoform of AFP in non-malignant liver diseases. AFP-L3 is the LCA-bound fraction and is the major glycoform of AFP in HCC. It can be detected in approximately 35% of patients with small HCC (<3 cm). The sensitivities of AFP-L3 in detecting HCC with cut off level of 15% range from 75% to 96.9% and specificities range from 90% to 92.0% correspondingly. Furthermore, some clinical researches have indicated that the high percentage of AFP-L3 is closely related to poor differentiation, biologically malignant characteristics including portal vein invasion of HCC and larger tumor mass.⁶

The half-life of AFP is approximately five to seven days. Following effective therapy, normalization of the serum AFP concentration over 25–30 days is indicative of an appropriate decline. This is the reason due to which our patient's AFP levels came down by 4 weeks in absence of HCC. The elevated AFP led to a suspicion for the presence of HCC, but the imaging studies demonstrated no evidence of a tumour. The serum AFP level can increase along with hepatic regeneration in viral hepatitis, but the elevation of the AFP levels in our case is much greater than what is generally known or expected. It could be assumed that the rise in AFP levels in our case was due to acute exacerbation of viral hepatitis and not due to presence of a tumour. It reflects disease activity of hepatitis.

Yao⁷ reported 3 cases with chronic hepatitis B infection who presented with initial serum AFP levels more than 1,000 ng/ml. There was no evidence of HCC based on multiple abdominal imaging studies. Initiation of antiviral drug led to rapid decrease in AFP levels in all 3 cases. This

suggests again that elevation of AFP was due to hepatic inflammation and viral replication.

Bae⁸ et al also reported 2 cases with HBV and HCV infection. AFP levels in both patients were more than 4700 ng/ml. AFP levels decreased in response to antiviral therapy, thus reinforcing that elevation was due to hepatic inflammation and viral replication.

The measurement of AFP is not sufficient for the diagnosis of HCC, and it may be elevated due to hepatic inflammation and viral replication. Such elevation usually reduces on response to antiviral therapy which should be considered.

CONFLICTS OF INTEREST

All authors have none to declare.

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