Measurement of Alpha-fetoprotein Levels in Patients with Chronic Hepatopathy

Eduardo Cienfuegos-Pecina, Diana P. Moreno-Peña, Paula Cordero-Pérez, Lucila C. Treviño-Lozano, Linda E. Muñoz-Espinosa, Ixel Domínguez-Vázquez, Gustavo R. Govea-Torres and Liliana Torres-González*

Department of Internal Medicine, Hepatology Center, "Dr. José E. González" University Hospital, Universidad Autónoma de Nuevo León, NL, México

Abstract

Introduction: Alpha-fetoprotein (AFP) is a glycoprotein associated with hepatic regeneration, as well as with neoplastic processes such as hepatocellular carcinoma (HCC). Nowadays, AFP is used as a criterion for HCC diagnosis, although it is not very sensitive and specific. **Objective:** The objective of this study was to evaluate the levels of AFP in patients with chronic hepatopathy. **Materials and Methods:** Patients with chronic hepatopathy and AFP were studied (January 2015-December 2017), including 160 patients. They were classified by etiology (primary biliary cholangitis, HCC, non-alcoholic steatohepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatitis B, hepatitis C, and liver disease of an indeterminate origin). **Results:** A significant difference was observed between the group of patients with HCC and the other study groups, presenting AFP levels above the reference limit. The other groups showed normal values. **Conclusion:** Patients with HCC showed high levels of AFP, but not patients with the other hepatopathies studied.

Key words: Alpha-fetoprotein. Hepatocellular carcinoma. Chronic hepatopathy.

Introduction

Alpha-fetoprotein (AFP) is a glycoprotein encoded by one of the genes of the albuminoid family (which, among others, includes albumin and the Vitamin D binding protein), located on the long arm of chromosome 4. AFP has a molecular weight of 69 kDa and is made up of three domains that give it a shape that resembles a "U".¹

This protein was discovered in 1956 by Bergstrand and Czar using electrophoretic techniques, demonstrating that it migrates between albumin and globulins and that it is expressed mainly during the embryonic period². It can be detected after the 1st month of pregnancy, being produced in the yolk sac and later in the

liver. In addition, small amounts of AFP are synthesized in the gastrointestinal tract³. It is produced in minimal quantities in an adult human, due to the strong methylation of its gene⁴. Its limited production is carried out by the oval liver cells that surround the bile ducts¹. In adult populations under 40 years of age, a normal AFP value of < 12 ng/mL has been reported^{5,6}.

In 1963, Abelev et al. demonstrated the production of AFP in mice with hepatoma, this being the starting point for further study as a tumor marker.⁷ Several reports in humans have shown that AFP increases during liver regeneration, especially after resection and massive hepatic necrosis⁸. Likewise, its production has been widely described as associated with neoplastic processes such as hepatocellular carcinoma (HCC)⁹. It

Correspondence:

Liliana Torres-González
E-mail: lilianator@gmail.com

Date of reception: 24-07 -2018
Date of acceptance: 30-10-2018
DOI: 10.24875/RMU.18000018

Available online: 18-01-2019
Medicina Universitaria. 2018;20(4):152-155
www.medicinauniversitaria.org

1665-5796/© 2018 Universidad Autónoma de Nuevo León. Published by Permanyer México SA de CV. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

has also been reported that AFP levels rise during the onset of chronic hepatopathies such as hepatitis C virus (HCV), hepatitis B virus (HBV), and hepatic cirrhosis without HCC and alcoholic hepatitis (AH)^{10,11}, autoimmune hepatitis (AIH)¹², and primary biliary cholangitis (PBC)^{13,14}. The correlation of AFP and hepatic steatosis has not been defined, having been reported that AFP by itself is not an adequate marker to predict the development of steatosis¹⁵.

Due to the relationship between AFP values and the presence of various diseases, it is important to know the elevation pattern of this marker in the most common hepatopathies. The objective of this study is to evaluate the levels of AFP in patients with chronic hepatopathy.

Materials and methods

A descriptive and retrospective study was carried out in patients of the Hepatology Center of the “Dr. José E. González” University Hospital of the Universidad Autónoma de Nuevo León. This study included patients with chronic hepatopathy and AFP determination from January 2015 to December 2017, considering the most recent value available in their file. AFP reference interval was considered to be between 0.89 and 8.78 ng/mL, according to the chemiluminescent micro-particle immunoassay methodology used to measure this marker¹⁶. The present investigation was approved by the Ethics and Institutional Research Committee with the number HI18-00001.

The patients were distributed according to their etiology in PBC, HCC, of origin to be determined (OOBD), non-alcoholic steatohepatitis (NASH), AIH, HBV, HCV, and AH. AFP levels of each etiology were compared to establish a statistical difference using an analysis of variance followed by the Tukey test for multiple comparisons using the Prism software (v. 6.0; GraphPad, San Diego, CA, USA). The results were expressed as a mean $\pm$ standard deviation and a value of $p < 0.05$ was considered a statistically significant difference between the means analyzed.

Results

The study included 160 patients. The characteristics of the population and its distribution by etiology are presented in table 1. The group of patients with HCC presented a concentration of 1819.00 ± 3070.00 ng/mL is higher than the AFP reference interval, while the other groups of patients with different hepatopathies showed levels within this range. The levels of AFP in the group

Table 1. Distribution of the studied population

Variable	Total population <i>n</i> (%)	Patients with HCC (%)
<i>n</i> (%)	160 (100)	10 (100)
Age (years) $\pm$ SD	50 $\pm$ 13.5	58 $\pm$ 14.24
Male	76	7
Female	84	3
PBC	11 (6.9)	-
HCC	10 (6.3)	10 (100)
OOBD	5 (3.1)	3 (30)
NASH	62 (38.8)	4 (40)
AIH	16 (10)	-
AH	3 (1.9)	-
HBV	36 (22.5)	1 (10)
HVC	17 (10.6)	2 (20)

PBC: primary biliary cholangitis; HCC: hepatocellular carcinoma; OOBD: of origin to be determined; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; AH: alcohol hepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus.

Figure 1. Alpha-fetoprotein levels according to chronic liver disease. PBC - primary biliary cholangitis; HCC - hepatocellular carcinoma; OOBD - of origin to be determined; NASH - non-alcoholic steatohepatitis; AIH - autoimmune hepatitis; AH - alcohol hepatitis; HBV - hepatitis B virus; HCV - hepatitis C virus.

*HCC versus study group, $p < 0.001$.

with HCC were higher than in the other study groups (PBC, OOBD, NASH, AIH, HBV, HCV, and AH, $p < 0.001$). No significant difference in AFP levels was found between the CBP, OOBD, NASH, AIH, HBV, HCV, and AH groups. AFP values in the distribution of patients according to hepatic etiology are shown in figure 1.

Discussion

AFP has been one of the most widely described biomarkers for the diagnosis of HCC, especially in patients

with chronic hepatopathy^{17,18}. However, despite the association between AFP and HCC, its real utility has been questioned because, by itself, it is considered a marker with variable sensitivity and specificity for HCC^{19,21}. The observed variability is due to the values determined by the technique used, the characteristics of the population, and the level of cutoff used^{22,23}. On the other hand, it has been reported that it is secreted up to 70% of patients with HCC, and according to various clinical guidelines, a value of > 200 ng/mL has been considered diagnostic criteria⁹. In addition, its usefulness for the prognosis of HCC treatment has been researched¹⁰. Sharma et al. demonstrated that AFP ratio/total tumor volume could predict the recurrence of HCC after surgical resection, with a value > 20 indicating a poor prognosis²⁴. Similarly, it was shown that a serum AFP value of < 15 ng/mL implied a significantly higher survival rate than that of patients with a higher AFP value²⁵. In the present study, levels higher than the reference interval (> 200 ng/mL) were observed in all the patients in the HCC group, which agrees with the reports that refer to it as a useful serum tumor marker for the diagnosis of HCC^{26,27}.

It has been described that the production of AFP is associated with a process of hepatocyte regeneration after an inflammatory process in diseases of a viral etiology²⁸. Therefore, it has been reported as elevated (> 700 ng/mL) in HBV cases²⁹. In the same way, a correlation between the concentration of AFP and the degree of necrosis and inflammation caused by HCV has been demonstrated. The increase in AFP concentration is not determined by viral load but by the magnitude of tissue damage³⁰. It has been reported that between 10% and 43% of patients with HCV show high levels of AFP^{13,31,32}. In the present study, the population of patients with HBV and HCV showed levels of AFP within the reference range established in this Hepatology Center, which differs with the aforementioned investigations.

It has been suggested that high values of AFP by themselves are mainly related to characteristic patterns of tissue damage in non-viral etiologies with AIH and AH. In a cohort of patients with AIH, an increase of AFP was reported while discarding the presence of HCC. However, this elevation was only observed in the acute phase of the disease¹². In other studies, an increase in AFP was observed in patients with AH in the acute liver damage stage at the beginning of the disease and then a decrease in the following stages to cirrhosis^{10,11}. In the present study, the groups of patients with AIH, AH, PBC, and NASH showed AFP levels within the reference

interval, which agrees with the reported studies, where there was no increase of AFP in the chronic stages.

Conclusion

Only the group of patients with HCC showed high levels of AFP, and the groups of patients with other hepatopathies had AFP levels within the reference range established in this Hepatology Center. In this study, it was observed that AFP serum continues to be a useful laboratory test to establish the absence or presence of HCC in various hepatopathies.

Conflicts of interest

The authors declare no conflicts of interest.

Financing

This project was financed entirely by own resources.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Mizejewski GJ. Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. *Exp Biol Med* (Maywood). 2001;226:377-408.
2. Bergstrand CG, Czar B. Paper electrophoretic study of human fetal serum proteins with demonstration of a new protein fraction. *Scand J Clin Lab Invest*. 1957;9:277-86.
3. Crandall BF, Lau HL. Alpha-fetoprotein: a review. *Crit Rev Clin Lab Sci*. 1981;15:127-85.
4. Kuo MT, Iyer B, Wu JR, Lapeyre JN, Becker FF. Methylation of the α -fetoprotein gene in productive and nonproductive rat hepatocellular carcinomas. *Cancer Res*. 1984;44:1642-7.
5. Christiansen M, Høgdall CK, Andersen JR, Nørgaard-Pedersen B. Alpha-fetoprotein in plasma and serum of healthy adults: preanalytical, analytical and biological sources of variation and construction of age-dependent reference intervals. *Scand J Clin Lab Invest*. 2001;61:205-15.
6. Ball D, Rose E, Alpert E. Alpha-fetoprotein levels in normal adults. *Am J Med Sci*. 1992;303:157-9.
7. Abelev GI, Perova SD, Khramkova NI, Postnikova ZA, Irlin IS. Production of embryonal alpha-globulin by transplantable mouse hepatomas. *Transplantation*. 1963;1:174-80.
8. Horn KD, Wax P, Schneider SM, et al. Biomarkers of liver regeneration allow early prediction of hepatic recovery after acute necrosis. *Am J Clin Pathol*. 1999;112:351-7.
9. Bruix J, Sherman M; Practice Guidelines Committee; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208-36.

10. Miller AI, Moral MD, Schiff ER. Presence of serum alpha-1-fetoprotein in alcoholic hepatitis. *Gastroenterology*. 1975;68:381-3.
11. Noble TE, Galdabini J, Resnik RM, Alpert E. Alcoholic liver disease. Absence of alpha-fetoprotein elevations in the recovery phase. *Dig Dis Sci*. 1980;25:248-51.
12. Yamagiwa S, Tamura Y, Takamura M, et al. Increase of fucosylated alpha-fetoprotein fraction at the onset of autoimmune hepatitis and acute liver failure. *Hepatol Res*. 2014;44:E368-75.
13. Tai WC, Hu TH, Wang JH, et al. Clinical implications of alpha-fetoprotein in chronic hepatitis C. *J Formos Med Assoc*. 2009;108:210-8.
14. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of Hbsag and anti-HCV status. *J Hepatol*. 2001;34:570-5.
15. Xu P, Xu CF, Wan XY, et al. Association between serum alpha-fetoprotein levels and fatty liver disease: a cross-sectional study. *World J Gastroenterol*. 2014;20:11865-70.
16. Abbott Laboratories. Architect System AFP. Abbott Park, IL, USA: Abbott Laboratories; 2009.
17. Lai Q, Melandro F, Pinheiro RS, et al. Alpha-fetoprotein and novel tumor biomarkers as predictors of hepatocellular carcinoma recurrence after surgery: a brilliant star raises again. *Int J Hepatol*. 2012;2012:893103.
18. Fasani P, Sangiovanni A, De Fazio C, et al. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. *Hepatology*. 1999;29:1704-7.
19. Wong RJ, Ahmed A, Gish RG. Elevated alpha-fetoprotein: differential diagnosis-hepatocellular carcinoma and other disorders. *Clin Liver Dis*. 2015;19:309-23.
20. Giannini EG, Marengo S, Borgonovo G, et al. Alpha-fetoprotein has no prognostic role in small hepatocellular carcinoma identified during surveillance in compensated cirrhosis. *Hepatology*. 2012;56:1371-9.
21. Gambarin-Gelwan M, Wolf DC, Shapiro R, Schwartz ME, Min AD. Sensitivity of commonly available screening tests in detecting hepatocellular carcinoma in cirrhotic patients undergoing liver transplantation. *Am J Gastroenterol*. 2000;95:1535-8.
22. Huo TI, Hsia CY, Chu CJ, et al. The predictive ability of serum α -fetoprotein for hepatocellular carcinoma is linked with the characteristics of the target population at surveillance. *J Surg Oncol*. 2007;95:645-51.
23. Gad A, Tanaka E, Matsumoto A, et al. Ethnicity affects the diagnostic validity of alpha-fetoprotein in hepatocellular carcinoma. *Asia Pac J Clin Oncol*. 2005;1:64-70.
24. Sharma Y, Weaver MJ, Ludwig DR, et al. Serum alpha-fetoprotein level per total tumor volume as a predictor of recurrence of hepatocellular carcinoma after resection. *Surgery*. 2018;163:1002-7.
25. Martínez-Mier G, Esquivel-Torres S, Nava-Lacorte A, et al. Correlación de los niveles de alfafetoproteína sérica preoperatoria y sobrevida en el tratamiento quirúrgico del hepatocarcinoma en una unidad médica de alta especialidad en Veracruz, México. *Rev Gastroenterol Mex*. 2017;82:357-60.
26. Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. *Clin Liver Dis*. 2001;5:145-59.
27. Hernández JC, Samada M, Roque A, et al. Valor diagnóstico de la alfa-fetoproteína en el carcinoma hepatocelular. *Biotechnol Apl*. 2011;28:34-9.
28. Cheng HT, Chang YH, Chen YY, et al. AFP-L3 in chronic liver diseases with persistent elevation of alpha-fetoprotein. *J Chin Med Assoc*. 2007;70:310-7.
29. Patil M, Sheth KA, Adarsh CK. Elevated alpha fetoprotein, no hepatocellular carcinoma. *J Clin Exp Hepatol*. 2013;3:162-4.
30. Chan SL, Mo FK, Johnson PJ, et al. New utility of an old marker: serial alpha-fetoprotein measurement in predicting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy. *J Clin Oncol*. 2009;27:446-52.
31. Soresi M, Magliarisi C, Campagna P, et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. *Anticancer Res*. 2003;23:1747-53.
32. Hu KQ, Kyulo NL, Lim N, et al. Clinical significance of elevated alpha-fetoprotein (AFP) in patients with chronic hepatitis C but not hepatocellular carcinoma. *Am J Gastroenterol*. 2004;99:860-5.