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Elevated AFP in the Absence of Hepatic Malignancy in a Patient with Acute Hepatitis

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Abstract: Alpha-fetoprotein is a tumor marker used in the clinical diagnosis and monitoring of treatment response in hepatocellular carcinoma (HCC). However, elevated levels are not specific for malignancy as it has been reported in other chronic liver diseases. This paper aims to describe such a case of elevated AFP in a case of acute hepatitis and its pathophysiology. Herein presents a 26-year-old Asian male with jaundice; who had no personal or family history of liver disease, drug or supplement use. The reported alcohol intake was not significant. The laboratory workup revealed hepatocellular type of liver injury (total bilirubin of 478 umol/L, direct bilirubin 401 umol/L, indirect bilirubin 77 umol/L, AST 1135 U/L, ALT 1592 U/L, LDH 53 U/L, ALP 139 u/L), elevated AFP (3337 IU/mL), elevated INR, positive autoimmune panel (ANA, Anti-Sm, Anti-TPO, Anti-TG). The serological examinations revealed a past infection with EBV and CMV, while imaging tests did not show ductal obstruction or the presence of mass lesions. A subsequent liver biopsy demonstrated interface hepatitis. The patient was then treated as a case of autoimmune hepatitis and was started on glucocorticoids with clinical and biochemical improvement including normalization of AFP levels.

Keywords: AFP, Case Report, Acute Hepatitis, EBV

1. Introduction

AFP has classically been used as a biomarker for HCC, and has also been included in the International Guidelines for HCC Surveillance [1-3]. However, it has been plagued by concerns of its low sensitivity and specificity in detecting HCC as the primary malignancy. There are also other benign causes of AFP elevation, especially in the setting of chronic liver disease. An article has recently been published on the development of novel markers, proposing their use instead of AFP for liver cancer diagnosis and monitoring for curative effect [4]. This case illustrates one such exemption. On the background of a previous EBV infection, patients can develop EBV hepatitis, EBV related autoimmune hepatitis, or autoimmune reaction to EBV. The history and the clinical profile of the patient are essential in directing the evaluation of these patients.

2. Case Report

2.1. Patient Information

A 26-year-old male seafarer, with no known comorbidities, was admitted for jaundice and tea colored urine. He denied any illicit drug use, blood transfusion, and smoking; likewise, there was no significant alcohol intake. His family history was likewise unremarkable.

2.2. Clinical Findings

The only pertinent physical examination finding was jaundice; there were no stigmata of portal hypertension.

2.3. Diagnostic Assessment

The initial impression was acute viral hepatitis. The workup revealed normal complete blood count, and deranged coagulation profile with an INR of 2.41. There is also note of

hepatic parenchymal pattern of injury (total bilirubin of 478 (NV 0-21 umol/L), direct bilirubin 401 (NV 0-5 umol/L), indirect bilirubin 77 (NV 0-16 umol/L), AST 1135 (NV 0-50 U/L), ALT 1592 U/L (NV 0-50 U/L), LDH 538 (NV 13-225 UI/L), ALP 139 (NV 35-130 UI/L)). The AFP was noted to be elevated at 3337 IU/mL, which prompted a more extensive evaluation (MRI of upper abdomen with MRCP: no bile strictures or dilatations, there was noted discrete periportal edema related to acute hepatitis; testicular ultrasound showed no gross lesion). Infectious causes were ruled out, but the patient showed titers for EBV IgG, VCA IgG, EBNA, PCR EBV and CMV IgG; implying the patient had history of previous infection. Autoimmune markers done revealed positive for anti-nuclear antibody (ANA) (titre: 1: 640 – speckled), anti-Smith (anti-Sm), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg). Metabolic profile revealed dyslipidemia (total cholesterol 6.33 mmol/L, triglycerides 2.56 mmol/L, HDL 0.59 mmol/L, and LDL 5.0) and a normal TSH.

Applying the Comprehensive Diagnostic Scoring System of the International Autoimmune Hepatitis Group [5], the patient was able to reach 13 points pre-treatment, and 15 points post treatment, thereby labelling the patient as probable autoimmune hepatitis.

An ultrasound guided core needle liver biopsy was done forty-two days into the steroid treatment but didn't reach the recommended adequacy criteria [6]. It revealed scanty fragmented liver tissues with a total aggregate diameter of 0.2cm. It had only about three partially distorted portal areas, which contained interface hepatitis. Plasma cells and eosinophils were not significantly noted. The ductal elements are not proliferated and cholangitis was not observed. There were also no portal granulomas seen. Liver cord disarray was difficult to ascertain due to the paucity of tissues. The hepatocytes however displayed hydropic changes. Cytoplasmic cholestasis was also seen. The paucity of findings on the liver biopsy may be due to the effect of the glucocorticoids or to the natural history of the disease.

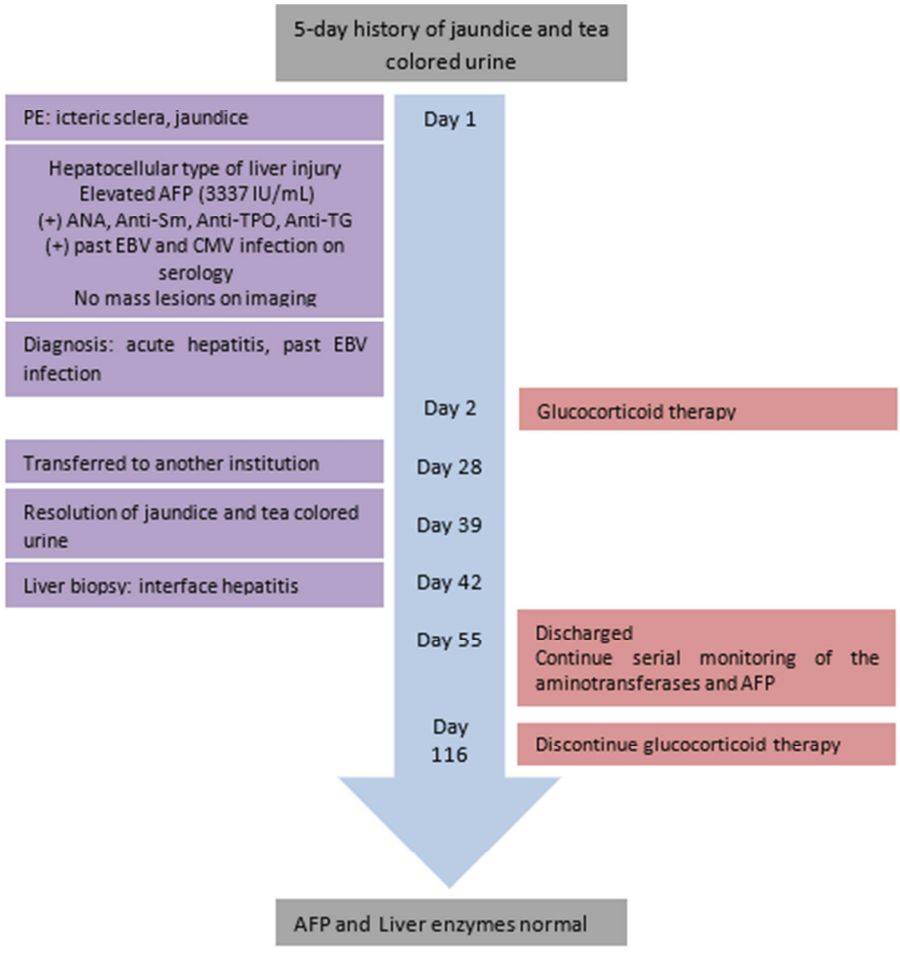
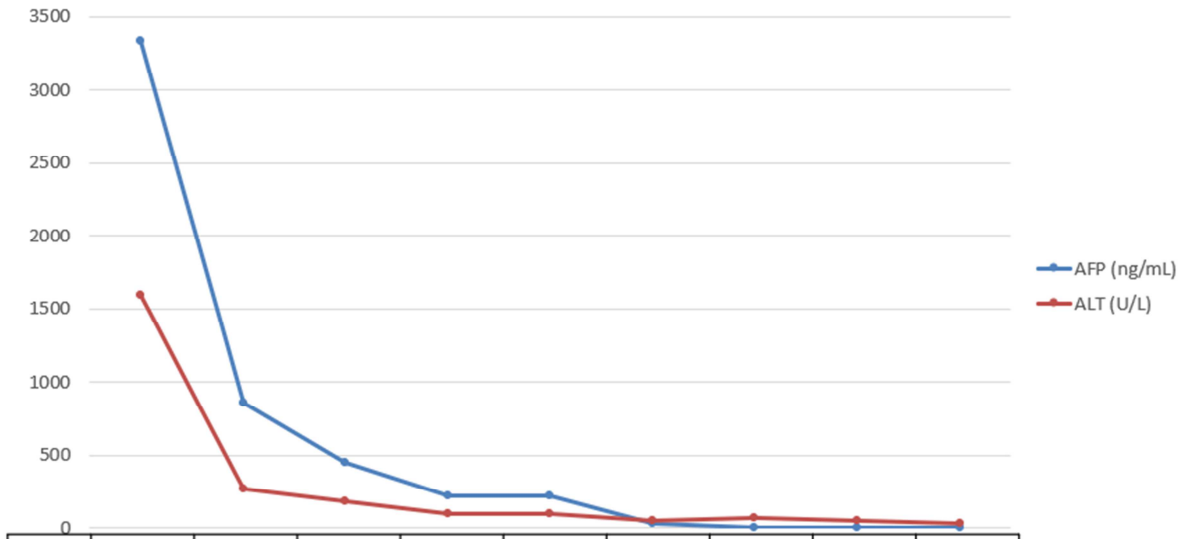


Figure 1. *Timeline of intervention and outcome.*

2.4. Therapeutic Intervention

Steroid therapy was started with prednisolone at 65mg/day (1mg/kg/day). The dose was subsequently decreased every 1-2 weeks, during which, there was resolution of the patient's jaundice and tea colored urine, with corresponding decrease in the levels of the serum AFP and biochemical liver tests. The figure below shows the trends in the ALT and AFP levels with therapy with steroids.



Day	1	28	33	39	45	55	84	115	135
Steroid mg/day	65	50	30	20	15	10	5	5 every other day	0

Figure 2. *Trend of AFP and ALT levels in relation to steroid dosage.*

3. Discussion

Elevation of AFP has been reported in many conditions including normal pregnancy, acute or chronic hepatitis, tyrosinemia, hepatoma, teratoma, other neoplasms of the primitive gut origin, murine graft vs host reactions and in lymphomas [7]. It is also used in the screening of fetal abnormalities including neural defects. A study by Bang et al., reported that AFP is pathologically elevated by the presence of germ cell tumors [8].

The application of AFP is widely recognized in the domain of HCC as it was been recommended as surveillance by APASL and the NCCN [9, 10]. In contrast, the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC), recommend against the use of serum AFP levels in combination with abdominal ultrasonography in HCC surveillance schema [3]; while the AASLD suggests surveillance with US, with or without AFP every 6 months [11].

Particularly in the background of chronic liver disease, AFP can be raised when there is high level of hepatocyte regeneration but remains low in the majority of patients with cirrhosis in the absence of HCC [12]. Kelly et al summarized the limitations to the efficacy of AFP due to the following circumstances: there is a proportion of HCCs that don't secrete AFP (irrespective of size), elevated AFP can occur with chronic liver disease in the absence of HCC, and the variability of sensitivity and specificity depending on the cut off value used. This has caused AFP to fall out of favor as a screening test. It is still an ongoing challenge in the field of HCC surveillance to identify suitable serum markers and validate their use [9].

Looking closely at the levels of AFP and its implications, with a normal value of <20ng/mL, a level of >1000 was the strongest pre transplant variable predicting HCC recurrence as well as vascular invasion according to Hameed et al [13]. In another study, the HCC differentiation, size and vascular invasion have strong correlation with AFP, while HCC size of ≥10cm and poor differentiation are independent predictors of elevated AFP [14]. Unfortunately, the studies on the cut off values are not only heterogenous, they are also used for prognostication of HCC rather than arriving at the primary diagnosis [3, 15]. In general, AFP levels in HCC are usually higher compared to different hepatopathies as demonstrated by Cienfuegos-Pecina et al. Their study showed that HCC patients presented with concentrations 1819±3070 ng/mL, while other chronic hepatopathies showed levels within the reference range [16]. Elevated AFP in AIH is not unheard of according to Wojtowicz-Chomicz et al, whose study included 359 patients with different chronic liver diseases to evaluate their serum concentrations of AFP. The highest AFP levels occurred in patients with autoimmune hepatitis (16.81±5.49 ng/mL), metastatic liver cancer (9.67±1.48 ng/mL), and liver cirrhosis (8.42±2.73 ng/mL) [17].

Studies have discussed the role of environmental triggers, for example, viral infections in the activation of AIH. Unfortunately, data is not very convincing [18]. It's not uncommon for EBV to cause a cholestatic form of hepatitis as described by Hinedi and Koff. These patients would present with fever, jaundice and malaise. Though hepatic involvement is common in EBV infection, it varies in severity and fewer than 10% actually develop hepatitis. Chronic disease has, so far, not been reported [19, 20].

Ideally, the liver biopsy in this case should have been done prior to the initiation of the glucocorticoid therapy. No paper has documented performing of the liver biopsy during or after treatment with immunosuppressants as to its histopathologic

findings.

The association of EBV with AIH has been reported before [21-24]. Theories on the relationship of EBV and autoimmune hepatitis include an EBV induced defect in the immunoregulatory functions of the suppressor or inducer T lymphocyte as it relates to the asialoglycoprotein receptor (ASGPR). This produces an antibody response to the EBV-ASGPR complex, inducing autoimmune hepatitis. The antibody response against EBV may also target the CD4+ T lymphocyte and be directly responsible for the functional impairment of the T cell [25, 26]. Other mechanisms may include immunodeficiency syndromes, complement deficiency, X-linked lymphoproliferative disease or treatment [20]. Though it appears that EBV is able to trigger autoimmune response, conclusive data linking causality to AIH is still lacking. Literature on the association of CMV with AIH is scarce. Kerkar et al did show a cross reactivity between 193-212 CYP2D epitope and homologues of HCV 2977-2996 and CMV 121-140 [27]. Since they share sequence homologies, viral infections with HCV and CMV can act as initiating factors of the disease in genetically susceptible patients [27, 28].

Fatigue is the usual clinical manifestation of hepatic involvement in EBV infection according to a case series by Mendez-Sanchez et al [29]. Other common manifestations include abdominal pain, nausea and diarrhea. However, the patient described in this case did not present with any of the typical symptoms. Though EBV is not a hepatotrophic virus, mildly elevated liver transaminases may occur. This is consistent with parenchymal type of injury rather than cholestasis. But severe cholestasis can also occur; the mechanism of which has been postulated to depend on the way the EBV infects human hosts causing a cytokine induced cholestasis [30].

4. Conclusion

This study demonstrated the low specificity of AFP as it relates to these unusually elevated levels even as compared to other studies on non-malignant cases of liver disease. In this patient with acute hepatitis, AFP elevation may represent hepatic regeneration. All of the features discussed further highlight the atypical presentation of the patient. The treatment of EBV related hepatitis is supportive, as most cases resolve spontaneously. Steroids and antiviral therapy are usually instituted in patients with severe hepatic involvement. In this case, the serologic and histopathologic results prompted the initiation of steroid therapy.

References

[1] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology (Baltimore, Md). 2005; 42 (5): 1208–36. Epub 2005/10/27. 10.1002/hep.20933.

[2] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology (Baltimore, Md). 2011; 53 (3): 1020–2. Epub 2011/03/05. 10.1002/hep.24199; PubMed Central PMCID: PMCPmc3084991.

[3] EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology. 2012; 56 (4): 908–43. Epub 2012/03/20. 10.1016/j.jhep.2011.12.001.

[4] Zhao Y, Ju Q, Li G. Tumors for hepatocellular carcinoma. Molecular Clinical Oncology. 2013 Jul; 1 (4): 593–598. Published online 2013 May 13. doi: 10.3892/mco.2013.119.

[5] The Royal College of Pathologists. Tissue pathways for liver biopsies for the investigation of medical disease and for focal lesions. The Royal College of Pathologists, 2008.

[6] Czaja A. J. (2016). Diagnosis and Management of Autoimmune Hepatitis: Current Status and Future Directions. Gut and liver, 10 (2), 177–203. https://doi.org/10.5009/gnl15352.

[7] Tomasi TB Jr. Structure and function of alpha-fetoprotein. Annu Rev Med. 1977; 28: 453-65. doi: 10.1146/annurev.me.28.020177.002321. PMID: 67821.

[8] Ball D, Rose E, Alpert E (1992) Alpha-fetoprotein levels in normal adults. Am J Med Sci 303: 157-159.

[9] Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the study of the liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010; 4 (2): 439–74. 27.

[10] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: hepatobiliary cancers. Version 2013. Fort Washington (PA): NCCN; 2013.

[11] Heimbach, J. K., Kulik, L. M., Finn, R. S., Sirlin, C. B., Abecassis, M. M., Roberts, L. R.,… Marrero, J. A. (2017). AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology, 67 (1), 358-380. doi: 10.1002/hep.29086.

[12] Kelly, S. L., & Bird, T. G. (2016). The Evolution of the Use of Serum Alpha-fetoprotein in Clinical Liver Cancer Surveillance. Journal of immunobiology, 1 (4), 1000116. https://doi.org/10.4172/2476-1966.1000116.

[13] Hameed, B., Mehta, N., Sapisochin, G., Roberts, J. P., & Yao, F. Y. (2014). Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society, 20 (8), 945–951. https://doi.org/10.1002/lt.23904.

[14] Liu C, Xiao GQ, Yan LN, et al. Value of α-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. World Journal of Gastroenterology. 2013 Mar; 19 (11): 1811-1819. DOI: 10.3748/wjg.v19.i11.1811.

[15] Fatourou EM, Suddle AR, Heneghan MA. Alpha-fetoprotein as a predictor of hepatocellular carcinoma recurrence following liver transplantation. Hepatoma Res 2018; 4: 63. http://dx.doi.org/10.20517/2394-5079.2018.62.

[16] Cienfuegos-Pecina, Eduardo & Moreno-Peña, Diana & Cordero-Pérez, Paula & Treviño-Lozano, Lucila & Muñoz-Espinosa, Linda & Domínguez-Vázquez, Ixel & Govea-Torres, Gustavo & Torres-González, Liliana. (2019). Measurement of Alpha-fetoprotein Levels in Patients with Chronic Hepatopathy. Revista Medicina Universitaria. 20. 10.24875/RMU.18000018.

[17] Wójtowicz-Chomicz K, Cichoz-Lach H, Lis E, Kowalik A, Słomka M. Ocena stezenia alfa-fetoproteiny u pacjentów z przewlekłymi schorzeniami watroby [Evaluation of alpha-fetoprotein concentration in patients with chronic liver diseases]. Pol Merkur Lekarski. 2012 Jun; 32 (192): 374-7. Polish. PMID: 22891562.

[18] Sebode, M., Hartl, J., Vergani, D., & Lohse, A. W. (2017). Autoimmune hepatitis: From current knowledge and clinical practice to future research agenda. Liver International, 38 (1), 15–22. doi: 10.1111/liv.13458.

[19] Hinedi TB, Koff RS. Cholestatic hepatitis induced by Epstein-Barr virus infection in an adult. Dig Dis Sci. 2003 Mar; 48 (3): 539-41. doi: 10.1023/a:1022592801060. PMID: 12757167.

[20] Modesto Dos Santos V, Da Costa Arruda Z Jr, De Farias Polcheira M, Da Silva De Souza DW, Rodrigues Oliveira Santos AM, Santos Corrêa Da Costa M. Hepatitis aguda por mononucleosis infecciosa en un varón de 21 años [Acute hepatitis due to infectious mononucleosis in a 21-year-old-man]. Rev Med Chil. 2013 Jul; 141 (7): 917-21. Spanish. doi: 10.4067/S0034-98872013000700012. PMID: 24356741.

[21] Saadah, O. I., & Bokhary, R. Y. (2013). Anti-mitochondrial antibody positive autoimmune hepatitis triggered by EBV infection in a young girl. Arab Journal of Gastroenterology, 14 (3), 130–132.

[22] Peng, H., Lim, T., Nam, J., & Lee, J. (2019). Autoimmune hepatitis following Epstein-Barr virus infection: a diagnostic dilemma. BMJ Case Reports, 12 (7), e229615. doi: 10.1136/bcr-2019-229615.

[23] Zellos, A., Spoulou, V., Roma-Giannikou, E., Karentzou, O., Dalekos, G. N., & Theodoridou, M. (2013). Autoimmune hepatitis type-2 and Epstein-Barr virus infection in a toddler: art of facts or an artifact? Annals of Hepatology, 12 (1), 147–151. doi: 10.1016/s1665-2681(19)31398-5.

[24] Vento, S., Guella, L., Mirandola, F., Cainelli, F., Di Perri, G., Solbiati, M.,… Ferraro, T. (1995). Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. The Lancet, 346 (8975), 608–609. doi: 10.1016/s0140-6736(95)91438-2.

[25] Mahalingam, M. (1995). Epstein-Barr virus and autoimmune hepatitis. The Lancet, 346 (8979), 913. doi: 10.1016/s0140-6736(95)92763-8.

[26] Rigopoulou EI, Smyk DS, Matthews CE, Billinis C, Burroughs AK, Lenzi M, Bogdanos DP. Epstein-barr virus as a trigger of autoimmune liver diseases. Adv Virol. 2012; 2012: 987471. doi: 10.1155/2012/987471. Epub 2012 May 28. PMID: 22693505; PMCID: PMC3368154.

[27] Kerkar N, Choudhuri K, Ma Y, Mahmoud A, Bogdanos DP, Muratori L, Bianchi F, Williams R, Mieli-Vergani G, Vergani D. Cytochrome P4502D6 (193-212): a new immunodominant epitope and target of virus/self cross-reactivity in liver kidney microsomal autoantibody type 1-positive liver disease. J Immunol. 2003; 170: 1481–1489.

[28] Manns MP, Johnson EF, Griffin KJ, Tan EM, Sullivan KF. Major antigen of liver kidney microsomal autoantibodies in idiopathic autoimmune hepatitis is cytochrome P450db1. J Clin Invest. 1989; 83: 1066–1072.

[29] Méndez-Sánchez N, Aguilar-Domínguez C, Chávez-Tapia NC, Uribe M. Hepatic manifestations of Epstein-Barr viral infection. Ann Hepatol. 2005 Jul-Sep; 4 (3): 205-9. PMID: 16177662.

[30] Shaukat A, Tsai HT, Rutherford R, Anania FA. Epstein-Barr virus induced hepatitis: An important cause of cholestasis. Hepatol Res. 2005 Sep; 33 (1): 24-6. doi: 10.1016/j.hepres.2005.06.005. Epub 2005 Aug 19. PMID: 16112900.