Case Report
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Extreme Alpha Fetoprotein Level and Parathyroid Hormone-Related Peptide Paraneoplastic Syndrome: A Unique Case Report of Hepatocellular Carcinoma

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ABSTRACT

Tumor markers and paraneoplastic hormones are key investigative tools utilized for diagnosis, prognosis and at times response to treatment in patients with suspicion or diagnosis of malignancy. In the setting of hepatocellular carcinoma, the use of alpha fetoprotein for preclinical detection, prognosis and response to treatment has been readily utilized for over 40 years. In combination with ultrasonography, alpha fetoprotein is also used for surveillance. Serum AFP levels >400 ng/mL in a high-risk patient are nearly diagnostic of HCC, with a specificity of >95 percent. Other tumor markers which have been found to be associated with hepatocellular carcinoma include des-gamma-carboxy prothrombin and lens culinaris agglutinin-reactive AFP (AFP-L3), but very few cases report parathyroid hormone related peptide to be associated with this malignancy specifically. We present a rare relationship between hepatocellular carcinoma and parathyroid hormone related peptide in the setting of extreme elevation of alpha fetoprotein at a level above 500,000 ng/mL.

Keywords: *Hepatitis, Hepatitis C, Hepatocellular Carcinoma, Alpha Fetoprotein, PTHrP, AFP, Parathyroid Related Protein*

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer related death worldwide, accounting for 80% of primary liver carcinomas (Bai *et al*., 2017). The highest prevalence of HCC occurs in low resource countries such as Eastern Asia and East African countries (Chung *et al*., 2009). HCC is a relatively preventable disease as there are many strong risk factors associated with its development, such as Hepatitis B (HBV), Hepatitis C (HCV), non-alcoholic fatty liver disease, alcohol abuse disorder, and toxin exposure (Bai *et al*., 2017). The use of blood biomarkers to detect and track the treatment response in HCC is important in diagnosing and treating HCC. This is typically done through alpha fetoprotein (AFP) levels, as they have been associated with increased cell proliferation (Park and Park, 2011). Many studies have been completed evaluating the sensitivity and specificity of AFP for HCC.

While cutoff points from 20 ng/ml to 400 ng/mL were evaluated, sensitivity ranges from 20-71.4% and specificity ranges from 80-100% (Chang *et al*., 2013). However, not all HCC is AFP positive. Half of HCC has shown to be AFP secreting, which is associated with higher rates of female patients, a younger age, higher association with HBV, larger tumors, lower differentiation grade, and lower overall survival. (Omata *et al*., 2008)

The most common paraneoplastic syndromes associated with HCC are hypercholesterolemia, hypoglycemia, erythrocytosis, and hypercalcemia (Rome *et al*., 2013). Recent studies have demonstrated that there may be an association between certain subtypes of HCC and hypercalcemia of malignancy (Roskams *et al*., 1993). Sclerosing hepatocellular carcinoma has been the most associated with elevated PTHrP levels and hypercalcemia (Saleem *et al*., 2016). Albar *et al*. utilized immunohistochemistry to examine the presence of PTHrP in a case of sclerosing hepatic carcinoma obtained at autopsy, they found that the neoplastic tissue displayed cytoplasmic immunostaining diffusely with the antibodies against PTHrP. Also, this manifestation has been found to be associated with a worse prognosis. Luo, *et al*. (1999) reported in a cohort study, 19.4 percent of patients with HCC developed paraneoplastic syndromes and subsequently were found to be less likely to be eligible for active treatment thus reducing survival.

We present a case of a patient with significantly elevated AFP levels and hypercalcemia secondary to production of PTHrP. Our goal is to contribute to the literature in hopes that PTHrP and extreme AFP levels could be considered as a diagnostic marker for malignancy in the setting of chronic liver disease.

Presentation of Case

A 67-year-old male with a past medical history of previously treated chronic hepatitis C, and alcoholic cirrhosis presented from his gastroenterologist office for worsening abdominal pain and distention. He underwent an outpatient MRI a week prior to presentation which revealed micronodular contour of the liver with multiple areas of hypoattenuation with possible fatty infiltration versus infiltrating lesions. Labs at that time revealed transaminitis and hypercalcemia. In the emergency department, he underwent a right upper quadrant ultrasound and portal venous doppler revealing some suspicion of at least 2 discrete focal masses at the right hepatic lobe as well as no flow detected at the right portal vein. During admission, the patient underwent a repeat MRI/MRCP which revealed similar findings of vague, somewhat nodular areas of altered signal predominantly involving the right lobe of the liver. His hypercalcemia and liver function tests continued to worsen, and a repeat right upper quadrant ultrasound revealed a right hepatic lobe mass measuring 9.5 cm by 8.8 cm which prompted a liver biopsy. Of note, the patient's PTHrP came back elevated with a normal 1,25 vitamin D as well as an AFP level of 508,806 ng/mL. Liver biopsy and pathology report demonstrated lesional cells to express HepPar1,

cytokeratin CAM 5.2, CD34, and CEA supporting the diagnosis of HCC. Staging CT of the chest revealed a single 3 mm right upper lobe nodule without any lymphadenopathy and no evidence of bone involvement on any imaging.

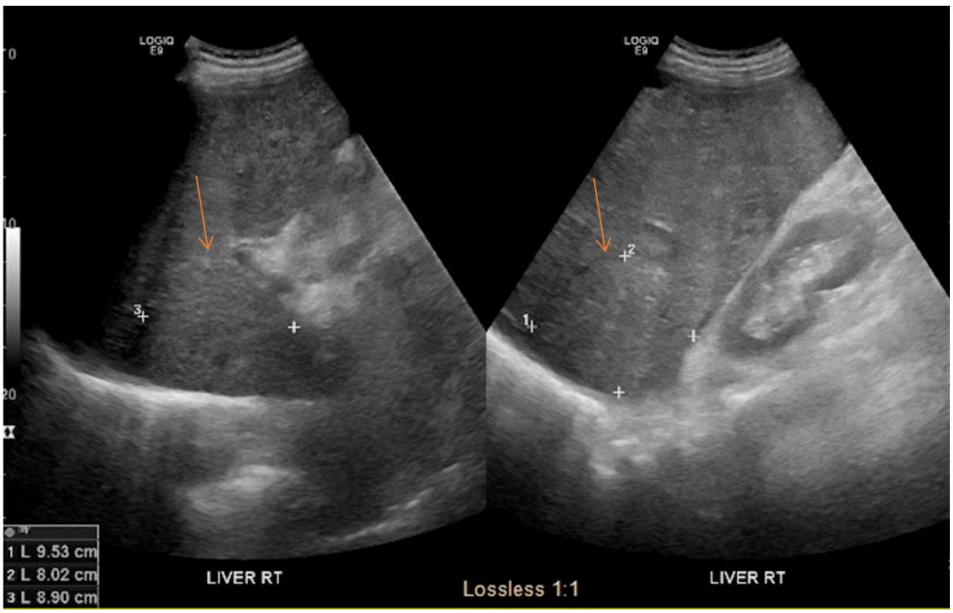

Figure 1: Repeat right upper quadrant ultrasound revealing right hepatic lobe mass (arrow).

Discussion

Our patient had a rare case of HCC with extremely elevated AFP levels and elevated PTHrP leading to hypercalcemia. In the setting of hypercalcemia of malignancy, it is important to differentiate if there is hypercalcemia due to bony metastasis or if it is due to PTHrP (Senturk and Cumali, 2007). PTHrP has demonstrated a significant role in hypercalcemia of malignancy (Wang and Zhang, 2020). Typically, it is associated with cholangiocarcinoma and used to differentiate between cholangiocarcinoma and HCC (Senturk and Cumali, 2007). However, PTHrP has been found in the fetal liver, but is typically not present in adults (Senturk and Cumali, 2007). While studies have been reported of AFP levels greater than 10,000 pg/ml without any sign of carcinoma, our patient demonstrated significantly higher levels with hypercalcemia (Yang *et al*., 2019).

Hypercalcemia due to PTHrP in the setting of HCC has been most often seen in the sclerosing HCC subtype (Yang *et al*., 2019). Omata *et al*. reported a hypercalcemia rate of 69% in patients with the sclerosing HCC subtype (Zhang *et al*., 2020). The increased biological activity of neoplastic hepatocytes may play a role in the increased production of PTHrP and its association with significantly higher AFP levels (Roskams *et al*., 1993). Chang, *et al*. (2013) found that hypercalcemia was the only paraneoplastic syndrome associated with more advanced TNM stage, higher disease burden, and poor prognosis

compared to hypercholesterolemia and erythrocytosis (Senturk and Cumali, 2007). It could be inferred that our patient likely did not have the sclerosing subtype due to the hypointense signaling on MRI, pathology results, and lack of many overlapping biomarkers (Wang and Zhang, 2020). This makes this presentation more unique in its associated hypercalcemia due to HCC without the sclerosing subtype. By reporting on this case, we hope to add to the current literature and raise awareness to the possibility of hypercalcemia of malignancy secondary to PTHrP. More data is necessary to aid in the investigation promptly in the setting of extreme AFP values to prevent disease progression or delay of care.

Conclusion

HCC is one of the most common causes of cancer-related mortality in the United States as well as around the world, with incidence rates continuously on the rise (Altekruse *et al*., 2009). Earlier detection may lead to earlier intervention and in-turn, hopefully a decrease in cancer-related morbidity and mortality. The necessity of additional tools to intervene sooner are needed to detect this disease at earlier stages. Tumor markers and paraneoplastic syndromes may aid in raising red flags before imaging modalities are obtained to expedite the diagnostic process and aid in facilitating earlier treatment plans.

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