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INTRAHEPATIC CHOLANGIOCARCINOMA WITH MARKEDLY ELEVATED SERUM ALPHA-FETOPROTEIN LEVEL- A RARE CASE REPORT

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ABSTRACT Hepatocellular carcinoma (HCC) is considered as the leading cause of primary liver malignancy, however, a tumor arising from the biliary tree should always be the differential diagnosis. Cholangiocarcinoma (CCA) is a group of primary liver malignancy that represents 10-20% of all primary liver masses with perihilar cholangiocarcinoma being the most common and intrahepatic cholangiocarcinoma (ICC) the less common subtype. The etiology of ICC is poorly understood however, alcoholic liver disease, hepatitis B and C virus infection has been implicated as a potential risk factor for ICC. Serum AFP is a commonly measured imperative biomarker. An elevated AFP >400 ng/ml is very unambiguous for HCC. On the contrary, AFP levels rarely surpass 20ng/ml in patients with intrahepatic cholangiocarcinoma. We report an unusual case of metastatic Intrahepatic cholangiocarcinoma with markedly elevated serum AFP levels to 37,686ng/ml and has no association with hepatitis or alcoholic liver disease.

KEYWORDS : intrahepatic cholangiocarcinoma, serum alpha-fetoprotein.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a malignant tumor instigating from peripheral intrahepatic bile duct epithelium. It is the second most common primary hepatic malignant tumor next to HCC. HCC represents more than 90% of all primary hepatic malignancies while ICC accounts for about 5% of all primary hepatic malignancies[1]. ICC is often an incidental radiologic finding. Due to the aggressive nature of ICC most cases are diagnosed with lymph node involvement, intrahepatic metastasis and peritoneal dissemination [2]. Although the etiology of ICC is not well understood, several risk factors have been suggested such as liver fluke infection, primary sclerosing cholangitis, hepatolithiasis, and asbestos [3]. Recently alcoholic liver disease, hepatitis B and C virus infection has been implicated as a potential risk factor for ICC [4,5]. AFP and protein induced by vitamin K absence or antagonist II (PIVKA II) are tumor markers of HCC, while CEA and CA 19-9 are tumor markers of ICC [6]. Elevation of Serum AFP (>20 ng/ml) is observed in 80% of HCC cases and about 20% of ICC cases, while only few cases of ICC show elevation of serum AFP to a level more than 1000 ng/ml [1].

In review of literature, we found only a handful of cases published with association of raised AFP in ICC. Here we report a unique case of Metastatic ICC in a 63-year-old male with a markedly elevated AFP (37,686 ng/ml) with no significant history.

Case Study

A 63-year-old man presented with pain in right hip from 1 month along with a decrease in appetite and loss of weight. There was no history of smoking and alcohol addiction. Laboratory investigations were negative for HBV and HCV.

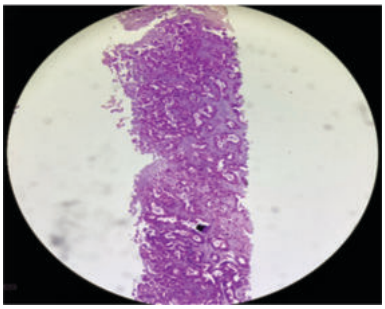

Fig1: Hematoxylin And Eosin Stained Slides Demonstrates Poorly-differentiated Adenocarcinoma(original Magnification 100x)

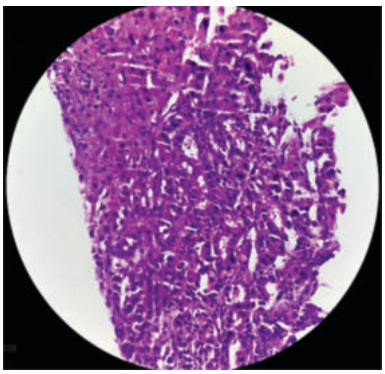

Fig2: Hematoxylin And Eosin Stained Slides Demonstrates Poorly-differentiated Adenocarcinoma With Adjacent Hepatic Parenchyma (Original Magnification 400x)

PET-CT was advised which showed multiple FDG avid lesions, predominantly in the right lobe of liver and minimum Gall Bladder thickening along with portocaval and skeletal metastasis. Pancreas were normal in size and echogenicity with no focal mass lesion. Pancreatic duct was also normal. Differential diagnosis of metastatic HCC and metastatic cholangiocarcinoma was made.

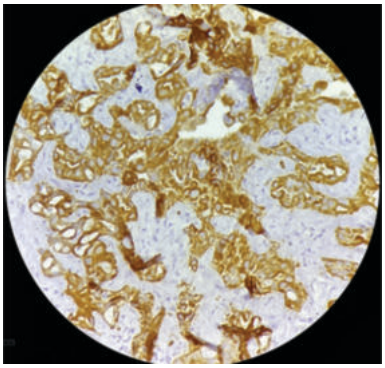

Fig 3:Immunohistochemistry: Diffuse Cytoplasmic And Membranous Positivity Of Ck-7(Original Magnification 400x)

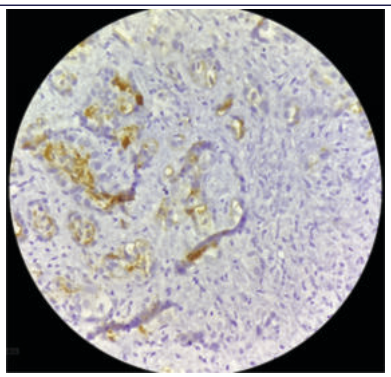

Fig 4: Immunohistochemistry: Focal Cytoplasmic Positivity Of Ca 19-9 (original Magnification 400x)

Hemogram was within normal range, however LFT was deranged (Total bilirubin- 8.59mg/dl, Direct bilirubin- 2.38mg/dl, Indirect bilirubin- 6.21mg/dl, SGPT- 122 U/L, SGOT- 268 U/L, Alkaline phosphatase- 500.02 U/L). Tumor markers CA-19-9 was within normal range (14.77 units/ml) however, AFP was markedly elevated to 37,686 ng/ml. Biopsy was done from hepatic lesion which showed features of Poorly differentiated Adenocarcinoma most likely biliary in origin. IHC reveals CK-7 and GATA-3 positivity with focal positivity of CA19-9 and negativity for CK-20, PAX-8, CDX2. Following these findings, a final diagnosis of Metastatic Cholangiocarcinoma was made.

DISCUSSION

CCA (Cholangiocarcinoma) is a group of primary liver malignancies that originates from biliary trees. It is the second most common primary hepatic malignancy next to HCC, comprising about 10-20% of all primary liver masses and 3% of gastrointestinal neoplasm [5]. CCA are divided into three main subtypes based on anatomic site of origin: intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (PCC), and distal cholangiocarcinoma (DCC). ICC originates above the second-order bile ducts, while extrahepatic PCC and DCC are titled by their insertion into cystic duct [7]. PCC accounts for the largest percentage, approximately 60% of all CCA, with DCC accounting for 30% and ICC accounting for only 6-10% [8].

ICC shares most of its risk factors with HCC. The major risk factors of ICC are primary biliary sclerosing cholangitis and primary biliary cirrhosis. Our case does not give any relevant history associated with these conditions. Other risk factors include congenital malformation of bile duct, hepatolithiasis, alcoholic liver disease, hepatitis B and C virus, smoking. Alcoholic liver disease, a major risk factor for HCC, has also been found to create a 3.92- fold risk for CCA [9]. Zhou YM et al ICC patients with positive AFP were associated with HBV infection and cirrhosis [10]. Our case has no association with alcoholic liver disease or hepatitis infection, still presented with a significantly raised AFP level of 37,686 ng/ml.

AFP is a fetal serum glycoprotein with 72kDa molecular weight. It is produced during gestation by fetal hepatocytes, yolk sac cells and gastrointestinal cells. It gradually begins to decrease to <10ng/ml by 300 days of birth. In 1963 AFP was first detected in serum of HCC patients. Since then it has been widely used for screening and clinical diagnosis of HCC [10]. Elevation of serum AFP has also been reported in other cancers like non-seminomatous germ cell tumor and carcinoma of stomach, colon, gallbladder, ovary, pancreas, lungs, kidney, duodenum, prostate and urinary bladder [11]. AFP producing ICC is extremely rare. According to a study done in Japan, out of 205 ICC cases only 4.9% measured elevated AFP levels greater than 1000 ng/ml, 1% had levels greater than 10,000 ng/ml and only 0.5% of patients had markedly elevated levels above 100,000 ng/ml [1,12]. So clinicians should be aware of this entity and should consider ICC as the differential of HCC with markedly raised AFP level.

The pathogenesis of ICC still remains indistinct. Alison et al suggested that ICC originates from hepatic stem cells also called hepatic oval cells [13]. They are a group of intrahepatobiliary cells, capable of differentiating to hepatobiliary cells and hepatic cells. When hepatic parenchyma is severely damaged or regeneration of hepatocytes is hindered by virus, drugs, toxins or carcinogens, oval cells are activated, proliferating and differentiating into hepatic and hepatobiliary cells to repair and reconstruct. It was demonstrated that hepatic oval cells strongly express AFP mRNA thus AFP is not only an indicator of cell de-differentiation but an important sign of hepatic stem cells [14].

Usually, due to an asymptomatic course CCA are diagnosed very late. It depletes viable treatment options and accounts for the shattering prognosis, with CCA representing about 2% of all cancer related mortalities. Despite their silent nature, CCA is highly aggressive and most often resistant to chemotherapy. This leaves surgery as the only viable option, however only about 25% are eligible for surgical resection. Most patients are diagnosed with advanced stage cancer or already have been metastasized at the time of diagnosis like our case (lymph node 43%, vascular-38%, Perineural-29%, biliary invasion-29%). For such non-resectable cases palliative treatment is initiated [9].

Due to the limitation in treatment options and advanced diagnosis of most ICC cases, the prognosis is miserable. Median survival is approximately 28 months with overall survival averaging around 30%. Even with surgery, the median overall survival is 51.1 months with relapse-free survival period of 24.4 months; however, the relapse rate was 60%. Patients with non-resectable tumors on palliative care, the overall survival is of 11.7 months and progression free survival of only 8 months. Despite continued research and growing knowledge, the 5-year survival rate still drifts around 7-20% [9].

CONCLUSION

Here we report an infrequent case of Intrahepatic cholangiocarcinoma with markedly raised AFP level to 37,686ng/ml and without any association with alcoholic liver disease or hepatitis. It is presented at an advanced stage with portocaval and skeletal metastasis.

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