Unusual presentation of fibrolamellar carcinoma: A rare case report

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ABSTRACT

Fibrolamellar hepatocellular carcinoma (fHCC) is a distinct type of first time used hence- hepatocellular carcinoma affecting particularly young patient with no gender predilection. However, there is increasing evidence of occurrence of this tumor in elderly patients also. Abdominal imaging with pre-operative biopsy provides accurate diagnosis. However, in difficult situations, CD68, cytokeratin 7, HepPar1, etc., immunohistochemical stains provide accurate diagnosis to differentiate this condition from other malignancies. Hereby, we present a case of fHCC in a 55-year-old female with equivocal imaging features and diagnosis was made by histopathology aided by immunohistochemistry.

Key words: *Arginase, CD68, Fibrolamellar hepatocellular carcinoma*

Fibrolamellar hepatocellular carcinoma (fHCC) is recognized as separate hepatic carcinoma in the WHO 2010 classification of tumors of gastrointestinal system [1]. This tumor particularly affects young age group with no sex predilection and lacks background liver disease [2]. Bimodal age distribution of fHCC is recently described [3]. Histopathology shows large polygonal cells arranged in the stroma composed of lamellar fibrosis. Few cells are eosinophilic due to prominent mitochondria [1]. Various immunohistochemistry (IHC) markers such as CD68, cytokeratin 7 (CK7), HepPar1, and arginase when positive help in diagnosis of fHCC [4]. We present a case of fHCC in a 55-year-old female with unusual imaging features. Definite diagnosis was made by histopathology combined with IHC.

CASE REPORT

A 55-year-old female presented with abdominal pain for 2 months. Pain was dull aching and dragging type. It was not associated with fever, vomiting, constipation, or diarrhea. She had no significant family or family history. On abdominal examination, abdomen was slightly enlarged and mass was felt on palpation, but further examination cannot be done due to tenderness.

Ultrasound examination showed abdominal mass; hence, she was further evaluated. On routine liver function test, she had total bilirubin; 1 mg/dl, aspartate transaminase; 196 IU/L, alanine transaminase; 34 IU/L, alkaline phosphatase; 184 IU/L; and gamma-glutamyltranspeptidase of 51 IU/L. She had reversal of albumin/globulin ratio with albumin of 2.4 g/dl and globulin of 4.9 g/dl. Her serum immunoglobulin G was raised (20.6 g/l) and hepatitis C virus-RNA and hepatitis B surface antigen were negative. Magnetic resonance imaging (MRI) of whole abdomen revealed a large lobulated mass measuring 15.5 cm × 11 cm × 4 cm × 148 cm in the left subdiaphragmatic space with heterogeneous post-enhancement (Figs. 1 and 2). Fat planes between mass and stomach were lost. The mass was having a very small connection with liver. Liver showed irregular outline with relative hypertrophy of left and caudate lobe. Considering these, the possibility of malignant gastrointestinal tumor was kept. Further, the lesion was showing areas of hypervascularity in arterial phase in peripheral parts with evidence of central scar. In equilibrium and hepatobiliary phase, there was heterogeneous spoke wheel-like pattern of enhancement. Considering these features, the possibility of fHCC was kept which may have pedunculated from the left lobe. Thus, to differentiate the two possibilities, the patient was further investigated. Other serum investigations done further showed a carcinoembryonic antigen (CEA); 2.14 ng/ml (normal range 0–5 ng/ml), CA19.9; 29.7 U/ml (normal range 0–37 U/ml), and mildly raised AFP; 11.64 ng/ml (normal range 0–8.5 ng/ml).

Hence, for confirmation, the core biopsy of mass was done. Biopsy on low power showed the cells with moderate to abundant cytoplasm arranged in the form of sheets, cords, ill-defined acini, and few singly scattered cells. The stroma showed fibrosis and was relatively hypocellular. On high power, the polygonal cells with hepatocytes differentiation were seen. They had round to oval pleomorphic, hyperchromatic nuclei with prominent nucleoli. Few of them were showing intranuclear vacuoles. Cytoplasm was granular and eosinophilic to clear. The stroma showed parallel lamellated fibers of collagen with spindle cells entrapped in between them (Fig. 3a and b). Thus, the possibility of gastrointestinal stromal tumor was ruled out.

IHC was done to confirm the diagnosis. Tumor cells showed cytoplasmic positivity for arginase 1 and canalicular-membranous immunostaining with polyclonal CEA indicating

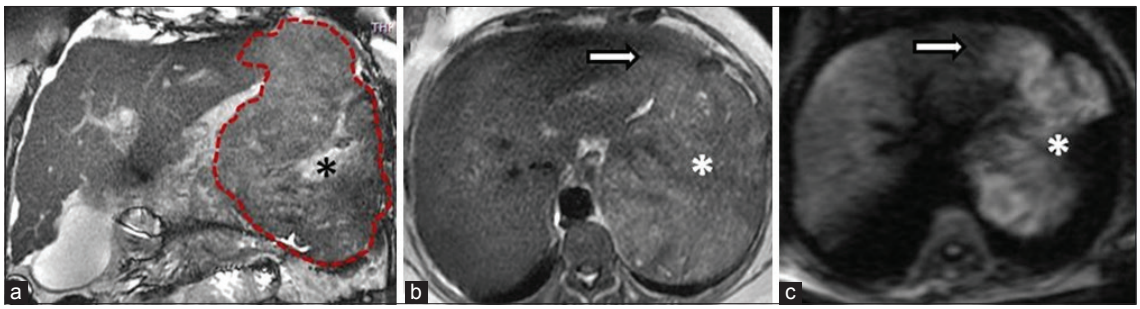

Figure 1: Non-enhanced magnetic resonance imaging images of the tumor (a) coronal balanced steady state free precession sequence depicting the extent of the heterogeneous soft tissue mass in the left subdiaphragmatic location, abutting the left lobe of liver (red dotted outlines of tumor margins)with a central hyperintense scar(*) (b) T2-weighted axial sequence of the upper abdomen demonstrating small area in left lobe of liver, segment II (bold arrow) showing heterogeneity of signal in contiguity with the left subdiaphragmatic mass lesion (*) (c) diffusion weighted sequence (b value=1000) showing restriction of the segment of liver (bold arrow) and the restricted signal of the mass lesion (*)

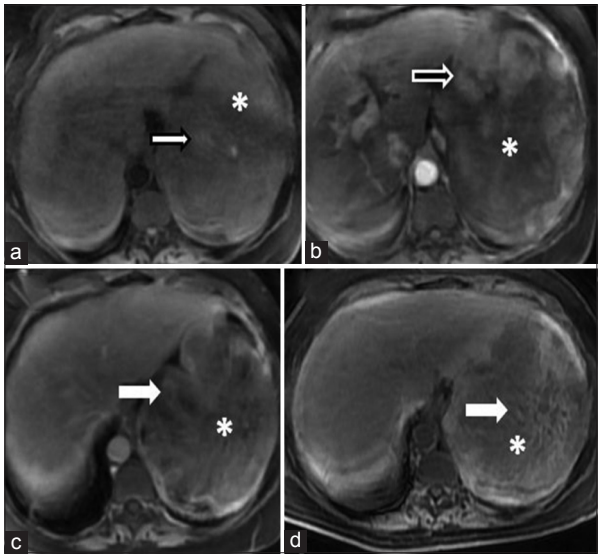

Figure 2: Dynamic contrast-enhanced magnetic resonance imaging (CEMRI) of the liver with hepatocyte specific contrast (Gd-BOPTA) (a) T1-weighted non-enhanced axial sequence of upper abdomen showing hyper intense area (bold white arrow with black outline) within the mass lesion (*) suggestive of hemorrhage (b) T1-weighted CEMRI axial sequence in arterial phase of the upper abdomen demonstrating areas of hyper vascularity (white arrow) in the peripheral portion of the left subdiaphragmatic mass lesion (*) (c) T1-weighted CEMRI axial sequence in equilibrium phase showing heterogeneous spoke wheel pattern like enhancement (bold white arrow) of the mass lesion (*) (d) T1-weighted CEMRI axial sequence in hepatobiliary phase showing diffuse hypointense signal of the mass (*) with heterogeneous spoke wheel pattern and partly enhancing central scar (bold white arrow)

hepatocytes differentiation [5-7]. Cytoplasmic positivity for CK7 was also present. IHC panel also included markers to exclude the differential diagnoses of combined hepatocellular-cholangiocarcinoma (stem cell markers and CD117) and adrenocortical carcinoma (vimentin and inhibit) were performed [8,9]. Tumor cells showed cytoplasmic granular positivity for CD68, whereas CD117, vimentin, and inhibit were negative (Fig. 4a-d). Hence, the tumor was finally labeled as fHCC. Tissue from the adjacent liver was not received; hence, histological confirmation of the parenchymal liver disease was not possible. The tumor was not amenable to surgical resection due to loss of fat planes with stomach. Considering the spread of the tumor, the patient was given palliative treatment but succumbed to death after 2 months.

DISCUSSION

The fibrolamellar carcinoma usually occurs in the young patients with normal background liver and has no sex predilection. Our patient was 55-year-old female with evidence of chronic parenchymal disease on MRI. Recently, fHCCs are also known to occur in elderly patients, leading to bimodal age distribution of this tumor [10]. They express both hepatocyte and bile duct IHC markers such as CK7, HepPar1, polyclonal CEA, and arginase 1 [4]. Along with these markers, they also commonly express CD68 [1]. CD68 is a glycoprotein which is commonly found in lysosomes and endosomes. Tumor cells in fHCC are rich in these organelles; hence are positive for CD68 IHC [11].

The scirrhous HCC was considered in differential diagnosis because the tumor was showing positivity for CK7 and arginase and was negative for HepPar1. Furthermore, the tumor had fibrous stroma, but the lamellated appearance of stroma with positivity for CD68 confirmed the diagnosis of the fHCC [12]. Similarly, combined hepatocellular and cholangiocarcinoma and adrenocortical carcinoma were ruled out with IHC [8,9]. The fHCC has a specific gene mutation, DNAJB1-PRKACA fusion. Both these are located on chromosome number 13, and their fusion gene is responsible for upregulation of PRKARCA gene [13]. The PRKACA is subunit of serine/threonine kinase. This kinase has a lot of cellular targets including mitochondrial biogenesis [14]. Tumor cells of fHCC are known to have increased mitochondria; hence, few of them show dense eosinophilic or oncocytic cytoplasm [15]. Thus, there must be some relation between PRKACA and this morphology.

Chung *et al.* in their study have described MRI features of fHCC. They found tumor to show increased enhancement on T1-weighed images. Central scar is not enhancing in the arterial phase similar to the present case [16]. HCC growing outside liver is known as exophytic or pedunculated HCC. They are usually larger due to enough space for growth in abdominal cavity. They arise from right lobe, left lobe, and inferior hepatic rim in the descending order of their frequency [17]. There is rare case report

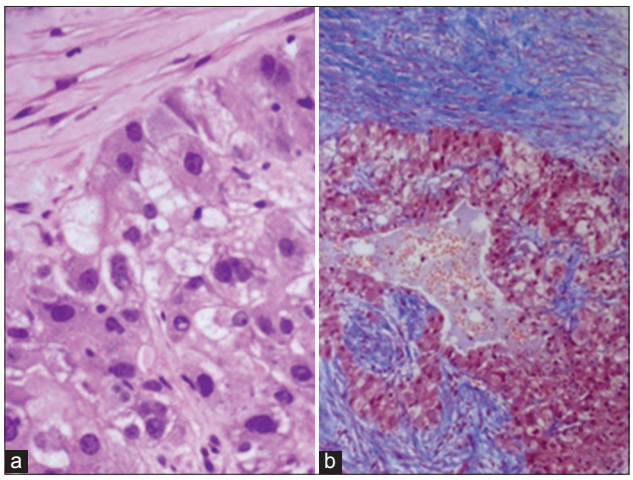

Figure 3: (a) ×400 view of hematoxylin and eosin stain of the tumor showing cells arranged in trabeculae. They have moderately pleomorphic, hyperchromatic nuclei with conspicuous nucleoli. Few nuclei show inclusions. Adjacent stoma shows fibers arranged in parallel fashion (b) ×100 view of Masson Trichrome stains to highlight the bundles of lamellar fibrosis running in tumor

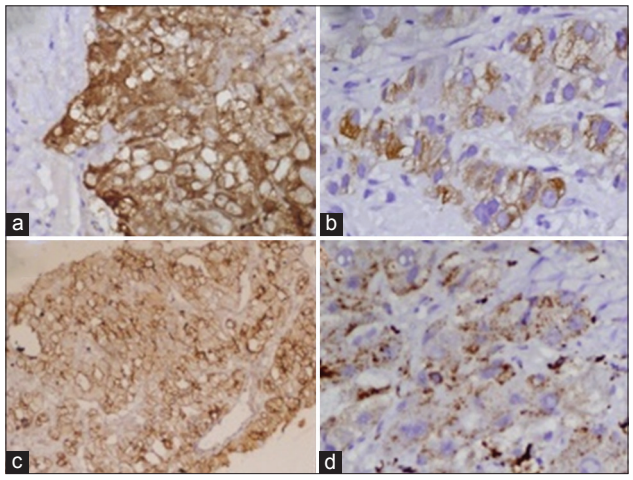

Figure 4: (a) ×400 view of arginase immunohistochemistry showing cytoplasmic positivity (b) CK7 immunohistochemistry is cytoplasmic positivity on ×400 view (c) ×100 view of polyclonal carcinoembryonic antigen showing canalicular-membranous positivity (d) ×400 view of CD68 immunohistochemistry is showing cytoplasmic granular positivity

of diagnostic dilemma between pedunculated HCC and adrenal metastasis. The authors have stated that as the tumor enlarges it becomes increasingly difficult to distinguish between adrenal and hepatic origin [18]. However, our large tumor was presenting as left-sided subdiaphragmatic mass, so the possibility of adrenal origin was low. Furthermore, we ruled out this possibility with the help of IHC.

The scirrhous HCC can resemble fHCC on imaging as both show delayed contrast enhancement due to significant fibrous component. Further, as scirrhous carcinoma is located commonly in subcapsular location, so it may also lead to pedunculated appearance [12]. The delayed enhancement is also seen in other tumors with fibrous component such as intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma. Thus, there is often diagnostic dilemma on imaging due to fibrous component. Central scar with delayed enhancement is also seen in focal nodular hyperplasia [19]. Finally, pre-operative percutaneous biopsy helps in accurate diagnosis of the condition.

Prognosis of fHCC is similar to the classic HCC in normal liver background, and their specific clinical features are not responsible for the better prognosis of disease [20]. As compared to the classic HCC, they are relatively less chemosensitive; hence, surgery is the main modality of treatment. There is increased chance of lymph node and peritoneal metastasis than classic HCC; hence, these tumors are more prone to recur [1]. Adjacent liver was not sampled in the biopsy in this case; hence, the MRI findings could not be confirmed on histology. The liver function tests were considerably abnormal. Deranged tests can also be due to the secondary effects of tumor in normal liver. Thus, although MRI showed evidence of chronic parenchymal liver disease, this case is labeled as fHCC in view of typical histological and IHC profile.

CONCLUSION

The diagnostic dilemma of equivocal radiology features can be solved by histopathology and ancillary techniques in a case of suspected HCC. The fHCC diagnosis can be confidently given in biopsy sample when there is the presence of classic histological features with positive immunopanel composed of CD68, arginase or HepPar1, and CK7.

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