ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 06, pp.4868-4871, June, 2019

DOI: https://doi.org/10.24941/ijcr.35663.06.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

FIBROLAMELLAR HEPATOCELLULAR CARCINOMA: A TWO YEAR STUDY AT A TERTIARY CARE CENTRE

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ARTICLE INFO

Article History:
Received 12th March, 2019
Received in revised form
17th April, 2019
Accepted 20th May, 2019
Published online 30th June, 2019

Key Words:
Fibrolamellar,
Hepatocellular,
Malignancy.

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ABSTRACT

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare variant of primary hepatocellular malignancy. It mainly affects younger adults and adolescents between 10 and 30 years of age. FL HCC differs from HCC in many ways such as patient demographics, presence and absence of common risk factors, tumor markers and prognosis. These tumors have typical radiographic findings which are confirmed by histopathology. We describe three cases of fibro lamellar carcinoma that were received in our department over a period of two years.

***Citation: Zubaida Rasool, Naheena Bashir and Imza Feroz,* 2019.** "Fibrolamellar hepatocellular carcinoma: a two year study at a tertiary care centre", *International Journal of Current Research*, 11, (06), 4868-4871.

INTRODUCTION

Fibrolamellar Hepatocellular Carcinoma (FLHCC) is a rare variant of primary hepatocellular malignancy arising in noncirrhotic livers of young individuals. Children and adolescents are also affected[1,2]. It accounts for 1 to 9% of all HCCs depending on the population studied.[3] The epidemiology shows that both genders are involved. FL HCC differs from HCC in many ways such as patient demographics, presence and absence of common risk factors, tumor markers and prognosis. Although some authors suggest that FLHCC is not a distinct entity but a morphological variant of classical HCC with prognosis similar to that of low grade HCC, most researchers now believe that FLHCC is a distinct form of liver cancer[3].These tumors have typical radiographic findings which are confirmed by histopathology. We describe three cases of fibrolamellar carcinoma that were received in our department over a period of two years

Case 1

30 year old woman presenting with vague abdominal pain, nausea, malaise and weight loss. On physical examination, vague abdominal mass was palpated. Serum analysis revealed mild elevation of beta HCG and fibrinogen levels. However, all the liver function markers were within normal limits.USG was performed which showed a well defined mass with heterogenous echogenecity. CECT done showed a 6x5 cm heterogenous, well defined mass with a lobulated outline. A CT guided biopsy was performed and a two linear bits measuring 1cm each was received by our department. Microscopically, the liver parenchyma was replaced by large polygonal and spindle shaped cells with deeply eosinophilic cytoplasm and prominent nucleoli arranged in cords surrounded by lamellated collagen fibers stained positive with masson's trichome stain. Hep Par stained the tumor cells positive showing the hepatic origin of tumor cells.

Case 2

20 year old female who presented with abdominal fullness, nausea, weight loss and night sweats. Physical examination revealed a huge palpable mass in the right upper quadrant. Serum analysis showed mildly elevated liver function enzymes.AFP was also mildly elevated. Beta HCG levels were normal. A CT scan performed revealed 11x10cm well encapsulated, heterogenous hepatic mass with central scarring. The lesion was hypodense showing marked enhancement after contrast injection. We received a 1cm biopsy bit which microscopically showed malignant hepatocytes that were well differentiated and polygonal with eosinophilic granular cytoplasm arranged in cords and trabeculae. These cells were surrounded by thick fibrous bands with stained positive with masons trichome. Non specific inflammation was present in the surrounding hepatic parenchyma.

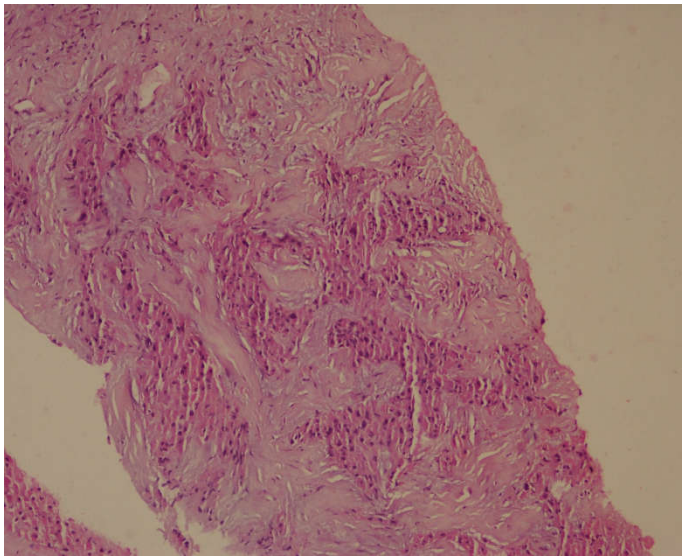

Fig. 1. Low power view of FL-HCC showing tumor cells arranged in trabeculae and cords separated by thick fibrous bands

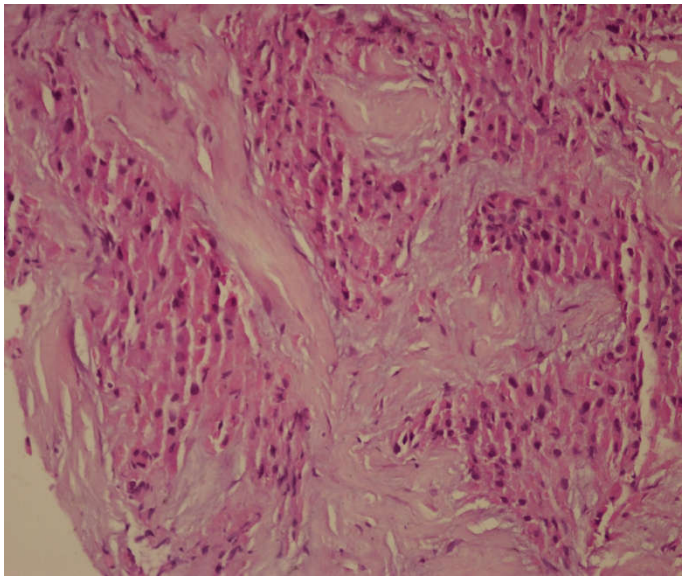

Fig. 2. High power view of FL-HCC showing polygonal cells with abundant eosinophilic cytoplasm encircled partially or completely by thick fibrous collagen bands

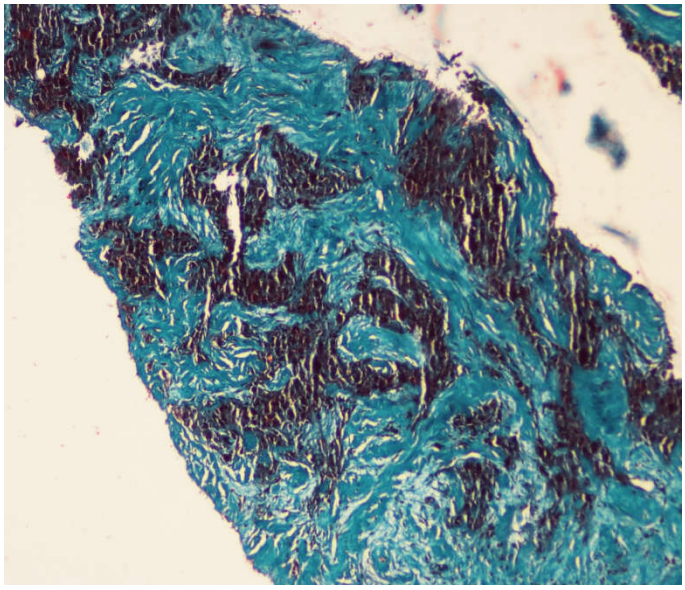

Fig. 3. Fibrous bands in FL-HCC satined positive with MTC stain

Case 3

A 15 year old male who presented with abdominal discomfort along with yellowish discoloration of skin. Physical examination revealed jaundice and a non tender hepatomegaly. A small 1x1cm swelling was palpated in the right breast. Serum analysis revealed elevated beta HCG levels. Bilirubin was 2.3mg/dl.Liver function enzymes and AFP levels were normal. Ultrasound showed a solitary irregular hypoechoic heterogenous mass measuring 8.5cm in the largest diameter in the left lobe of liver with distended portal vein. Splenomegaly was also found. FNAC of the right breast swelling revealed gynaecomastia. A CT abdomen showed hypoattenuating 9x8 cm lesion with calcifications and necrosis. A CT guided biopsy was done and received by our department. The biopsy was received in bits ranging in size from 1 to 0.5cm. Microscopically cells showed large nuclei with abundant and eosinophilic cytoplasm. The cells were arranged in a trabecular pattern and were separated by deposition of lamellated fibrous connective tissue.Neoplastic cells were observed corresponding to neoplastic thrombi. Bile was found in the tumor cells.Immunohistochemical studies showed positivity of the neoplastic cells for Hep-par, CK7 and CEA.

DISCUSSION

FLC accounts for between 1% and 9% of all HCCs depending on the population studied[3-11]. Typically, FLC affects younger adults and adolescents between 10 and 30 years of age, but recently an older patient group (70-79 years of age) was described after detailed analysis of the Surveillance, Epidemiology, and End Results (SEER) program in the United States, 2000-2010[12]. Compared with HCC, some studies note that FLC patients are more likely to be female, while others have noted no specific sex predilection[8,12,13]. All of the three patients in our study were young adults in the age range of 15-30 years. Two of our patients were females and the youngest was an adolescent male. The patients with fibrolamellar carcinoma present with non specific symptoms such as nausea, abdominal fullness or discomfort, weight loss, malaise and vague abdominal pain. Most common finding on physical examination is abdominal mass with or without pain in the right upper quadrant. Jaundice is seen in 40% of the patients[14]. All our patients had similar findings. Jaundice and hepatomegaly were however seen in the adolescent male only. Patients may present with rare symptoms like gynaecomastia in males[15], fulminant liver failure[16], recurrent deep vein thrombosis[17], encephalopathy[18], thrombophlebitis of the lower extremity[19], hypoglycaemia[20], recurrent obstructive jaundice[21] or biliary obstruction[22], paraneoplastic hyperthyroidism[23], severe anemia[24], the Budd– Chiari syndrome[25], massive ascites[26], shoulder pain[27], nonbacterial thrombotic endocarditis[28], liver abscess-like symptoms[29], metastatic lesions in other organs such as the bone[30]. The only male in our study presented with gynaecomastia. Serum levels of aspartate aminotransferase, alanine aminotransfearse and alkaline phosphatise can be elevated. Serum alphafetoprotein frequently elevated in HCC,is normal in most FL-HCC.Only 5-10% of FL-HCC cases are associated with alpha fetoprotein levels more than 200ng/ml.[31] Beta HCG can sometimes be elevated. Other serum findigs in patients with FLHCC include elevated transcobalamin I levels, transcobalamin 2 and vitamin B12 binding capacity[32,33]. The diagnosis is made on the basis of clinical symptoms, imaging and pathological findings. Imaging modalities that are helpful include ultasonography,

computed tomography and magnetic resonance imaging. On ultrasound FLC is characterised by well defined mass that has heterogenous echogeneticity. Ultrasound features of fibrolamellar carcinoma are however nonspecific.[34,35] More beneficial than ultrasound are CT and MRI. An unenhanced CT in a case of fibrolamellar carcinoma usually presents as large hypo attenuating mass. Calcification is commonly seen(65-80% of cases). Central stellate scar is often seen. The presence of stellate scar however is not pathognomic of fibrolamellar HCC and has been reported in many benign and malignant liver lesions. Necrosis may be seen but intratumoral hemorrhage is uncommon.[23,36] After iv administration of iodinated contrast material, most fibrolamellar HCCs show heterogenous hyper attenuation on arterial phase images. This is due to the presence of large hypervascular tumor cells surrounding hypovascular fibrotic bands CT scan that include an unenhanced phase followed by an arterial phase, portal venous phase and a delayed phase are recommended.

The cases in our study showed a similar picture with associated necrosis, calcification and scarring. At MR imaging fibrolamellar tumors are known to be hypointense to liver on T1 weighted images and hyperintense to liver on T2 weighted images. Calcification is generally not seen in MRI.[23,35]. None of our cases got MR imaging done during their diagnostic evaluation.While cross sectional imaging can strongly suggest fibrolamellar carcinoma, the actual diagnosis can only be achieved by the use of a biopsy. Macroscopically the cut surface of the tumor is bulging,white brown. Fibrous bands are seen throughout and a central stellate scar as seen radiologically is also present. Microscopically FL-HCC shows polygonal cells with large nucleoli and abundant eosinophilic cytoplasm encircled partially or completely by thick fibrous collagen bands which are positively stained with MTC stain. Some cases might show pale bodies (ground glass neoplastic hepatocytes which are PAS positive) and deposition of copper. The abundant granular eosinophilic cytoplasm is because of the abundant mitochondria in the cytoplasm. Vascular invasion and necrosis may be seen. Mitotic figures are less common than in usual hepatocellular carcinoma. All our cases had a typical microscopic picture. Immunohistochemically, FL-HCC shows CK7, EMA, CD68 and Hep Par 1 positivity[2,9,] The treatment of FLHCC is surgical resection with adequate lymph node dissection. Recurrence is reported in 30-100% of patients depending on duration of follow up and the type of surgery performed. The prognosis of FLHCC is still debatable. Many authors have reported FLHCC to have better prognosis than classic HCC, others have reported it to be similar to FLHCC.[37,38,39,40]

Conclusion

FLC has a different epidemiology, radiological appearance, as well as pathologic features than HCC. Most often, patients who present with FLC have an absence of common risk factors seen in classic HCC. While clinical features and laboratory markers are often not helpful to differentiate FLC from classic HCC, cross-sectional imaging with CT or MRI will typically display features highly suggestive of FLC. Histopathological diagnosis however, is most important for confirmation of diagnosis. For patients with resectable disease, the cornerstone for treatment is surgical resection with adequate lymphadenectomy. The long-term prognosis for patients with resected FLC is good; however, many patients will experience a recurrence.

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