



BMH Med. J. 2021;8(1):52-57. **Case Report**

Familial Hepatocellular Carcinoma In A Non Hepatitis B Endemic Area: A Case Report And Review Of Literature

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Abstract:

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide. The majority of the cases are Hepatitis B or C virus (HBV, HCV) related. Familial clustering of HCC is known in HBV endemic areas. There are also genetic alterations which have been identified in families with HCC in non endemic areas. We report such a family of two siblings diagnosed with HCC at a young age who presented to us. One patient had incurable disease and the other patient underwent curative surgery. We also review relevant literature of familial HCC through this case report.

Keywords: HBV related HCC, familial HCC

Introduction

Primary liver cancers comprise the sixth most common cancers occurring worldwide and include Hepatocellular carcinoma (HCC) which comprises of 90% of cases, and intrahepatic Cholangiocarcinoma which comprises of 10% of cases [1]. These tumors have a variable prevalence across geographical and racial groups. The highest incidence of HCC is seen in Asia and Africa and the incidence has been found to closely mimic the distribution of infections with Hepatitis B and C viruses (HBV, HCV) in these areas. The age adjusted incidence rates of HCC are the highest in the Southeast Asian countries of Korea, Thailand and Japan (37-47%) and the lowest in United Kingdom, Turkey and Iran (1.4-3.3%) [2].

The etiology of HCC varies according to the incidence rates with HBV infection and Aflatoxin exposure being the most common cause in high incidence areas and in contrast, HCV infections, alcohol ingestion and obesity and metabolic syndrome account for the most common causes in low incidence areas. Overall, the viral infections account for approximately 75-80% of the global burden of the disease. The other less common causes of HCC include metabolic disease (eg: Wilson's disease, Alpha 1 anti-trypsin deficiency etc) [3].

Familial occurrence of HCC in occurs most commonly in HBV endemic areas. This type of clustering of cases is especially seen in the Southeast Asian countries but less common in the West. However, a family history of liver cancer is a significant risk factor for the development of HCC in first degree relatives. Many chromosomal aberrations have been found frequently in HCC including amplifications of chromosomes 1q, 8q, 6p,17q and deletions of 8p, 16p, 4q, 17p indicating the key genes involved in carcinogenesis are tumor suppressor genes p53 or Rb [4].

We hereby report a case of two siblings with HCC and review relevant literature related to the rare familial occurrence of this tumor.

Case Report

We saw two siblings in our Out Patient Department, one a young male and another a young female. They had been referred with complaints of vague abdominal pain and symptoms of asthenia and loss of appetite and loss of weight. Their blood reports were unremarkable except for anemia in the sister. On preliminary imaging with a Transabdominal Ultrasonogram (USG), the female patient had evidence of multiple lesions scattered throughout the liver with vascularity pattern suggestive of Multiple HCCs. She underwent a Triphasic MRI – Liver which showed Hepatomegaly with multiple large lobulated lesions with relative washout on venous phases and faint scar enhancement on delayed images with capsular retraction in the right lobe and compression of hepatic veins suggestive of Fibrolamellar HCC. However, her Alpha Feto Protein (AFP) levels were found to be more than 1000 and she was found to be negative for CK17 and CD34 on Immunohistochemistry (IHC) of needle biopsy based on which diagnosis of well differentiated HCC was made. On account of inoperability of the tumor and non suitability for liver transplantation, she was planned for palliative chemotherapy. She has been on chemotherapy with Sunitinib since then, and is on regular follow up.

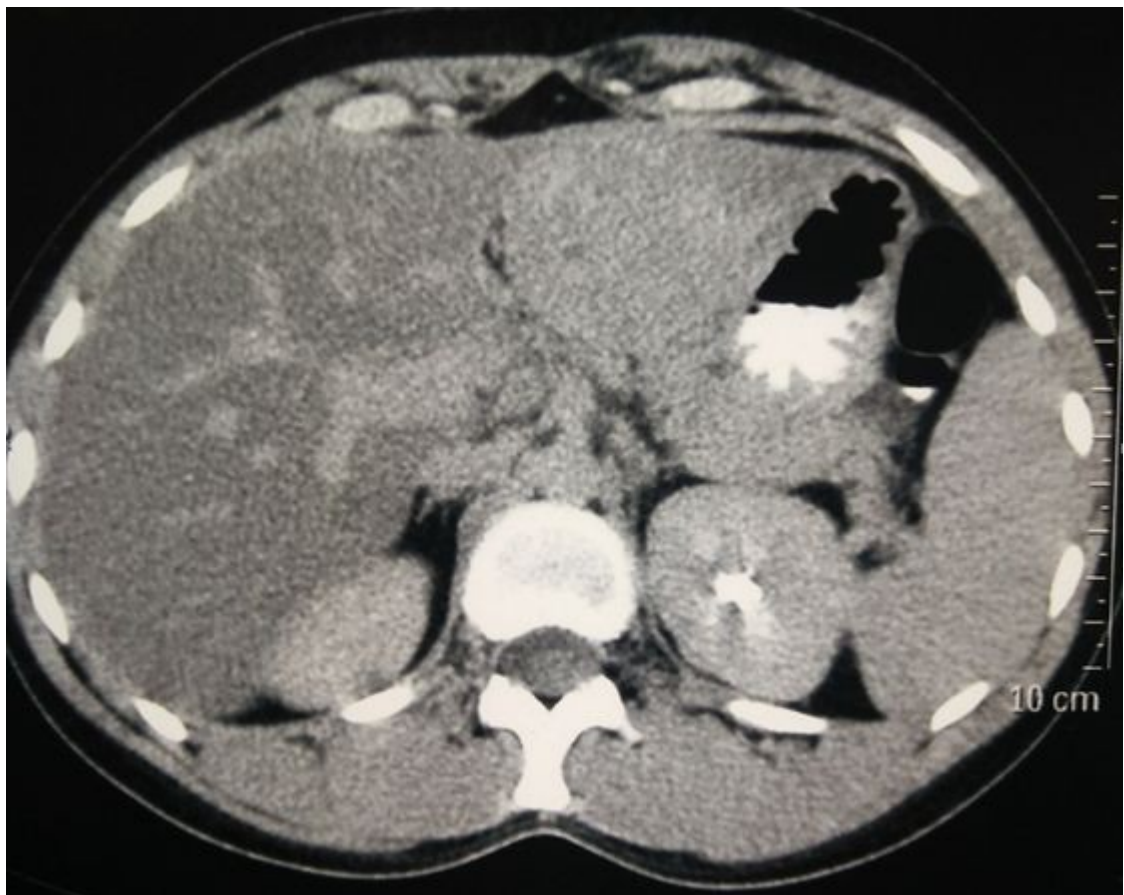


Figure 1: CT showing an exophytic HCC from the segment 3 of the liver

On the other hand, the male patient on USG had evidence of an exophytic lesion from the segment 3 of the liver with features of HCC. He underwent a Spiral CT which showed an exophytic HCC from the segment 3 of the liver with no evidence of vascular, adjacent organ involvement or distant metastasis (**Figure 1**). His AFP levels were 400IU/L. He was deemed operable and he underwent left lateral segmentectomy. Intraoperatively he was found to have a 5*5 cm well circumscribed tumor in the segment 3 of liver with no evidence of metastatic disease elsewhere with normal adjacent liver parenchyma (**Figure 2**). Post operatively he recovered well, had no complications and was discharged on the fifth postoperative day. On IHC, the tumor was found to be positive strongly for Hepar-1 and Glypican 3 (**Figure 3 a and b**) and negative for CK7 and CD68. On this basis, his final Histopathology examination was reported as moderately differentiated HCC with clear margins. He is now on regular follow up with us.

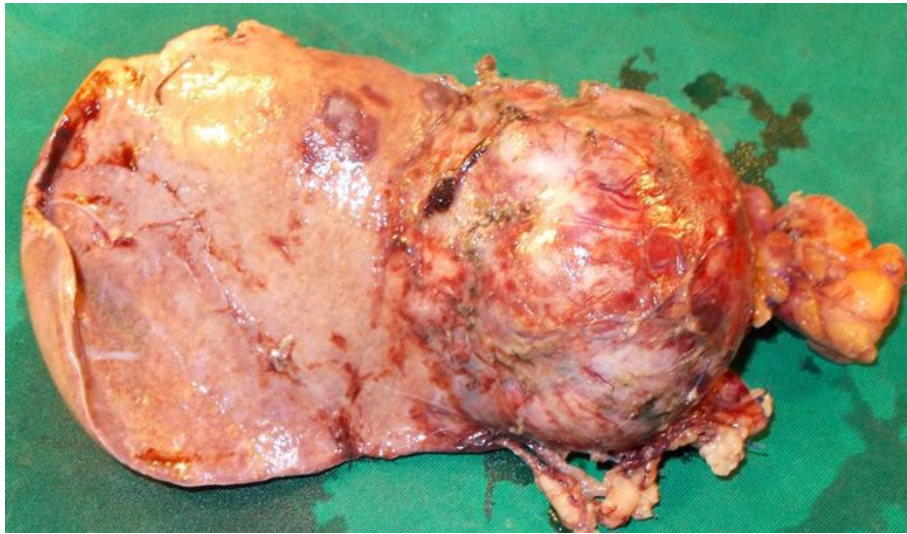


Figure 2: Circumscribed tumor excised from the segment 3 of liver

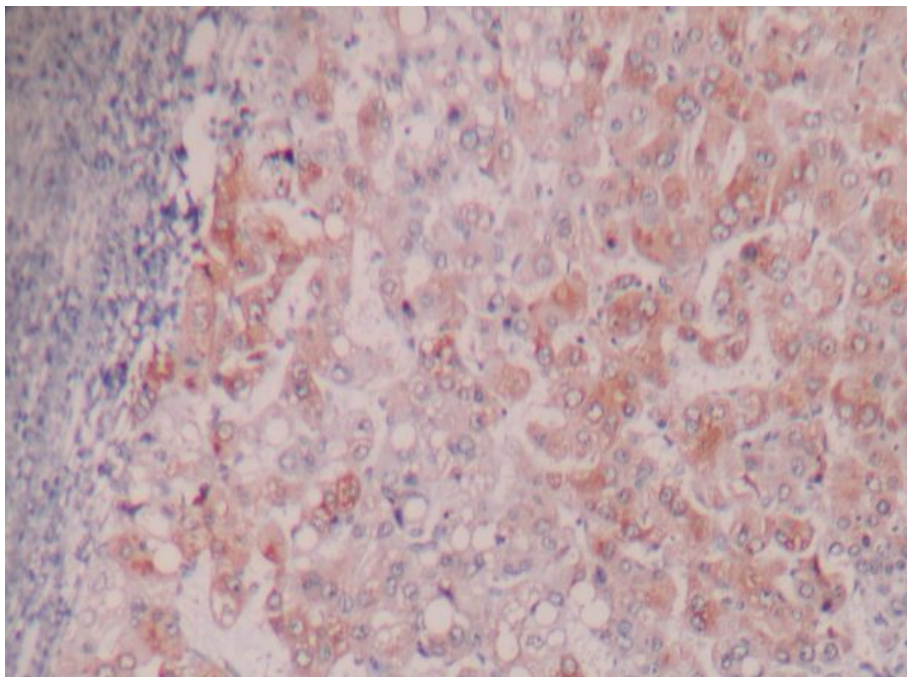


Figure 3a: Glypican 3 staining on IHC

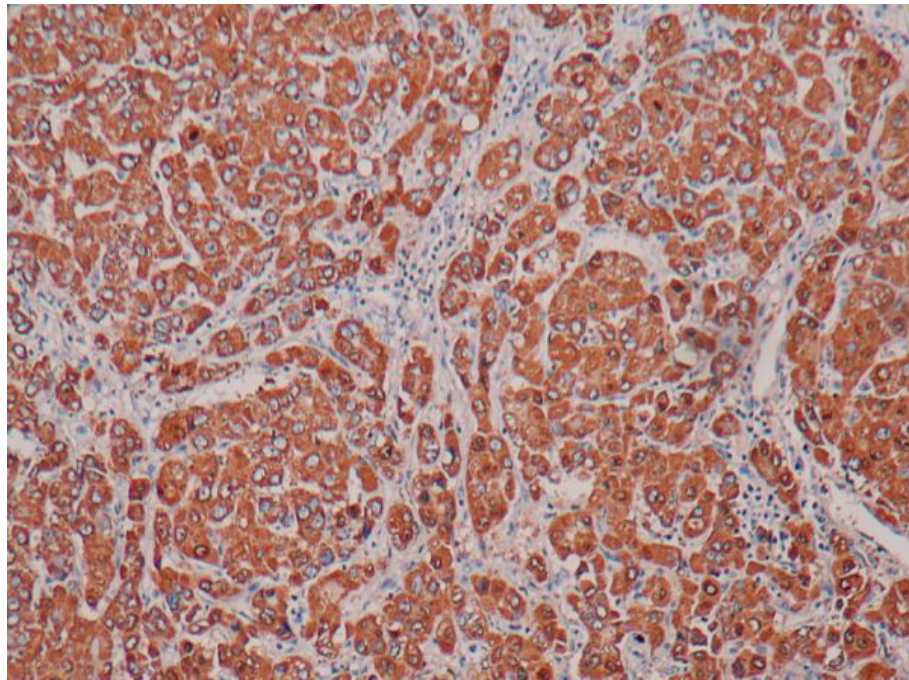


Figure 3b: Hepar 1 staining on IHC

Discussion

Hepatocellular carcinoma is a major health problem with a global burden of more than a million cases per year, with more than 3/4ths of the cases being reported from Asia and Africa [5]. In addition, the rising incidence in the developed countries is now related to HCV infection and the increasing prevalence of alcoholism and metabolic syndrome in the West. Majority of cases occur in the background of chronic hepatocyte injury with repeated attempts at regeneration leading to cirrhosis and then to dysplasia and then to carcinoma [5].

The Familial clustering of Hepatocellular carcinoma among family members is not a new entity. There have been multiple case report of similar occurrences in literature [6]. The majority of cases reported in literature have been noted in areas endemic for HBV or HCV infections, importantly, the Southeast Asian countries [7]. The higher incidence in these areas has been related to younger age of contracting infection thereby establishing a chronic carrier state in these patients. The transmission of infection may be from maternal to offspring or it may be related to poor hygiene practices prevailing in these developing countries [7]. Studies about the mechanism of HBV induced hepatocarcinogenesis demonstrate a wide array of genetic alterations. Basically there is a process of insertional mutagenesis that contributes to the alteration in the genome leading to development of HCC. Studies however indicate that cirrhosis is not a prerequisite for the development of HBV related HCC [8]. In addition, there is a high risk of development of HCC in first degree relatives of patients who are HBV carriers with an Odds ratio of 2.57 in comparison to controls as reported in a population based study from China [9]. The mechanism of carcinogenesis in aflatoxin related HCC has been due to direct mutations in the p53 gene [5]. The mechanisms in other causes of HCC, namely, Wilson's disease, hemochromatosis and other metabolic disorders are related to poorly controlled immune responses [4].

Familial clustering of HCC is also noted outside the endemic areas. In these patients, a wide variety of genetic alterations have been identified. In addition, genetic studies indicate that development of HCC is a multistep process proceeding from regenerative nodules to low grade dysplasia to high grade dysplasia to early HCC. The main process changing the tumor from a static HCC to a progressive HCC is the development of neovascularization thereby changing the blood supply from a portal venous to a hepatic arterial predominant type leading to typical features of HCC on imaging. The most common molecular mechanisms

involved are Loss of heterozygosity (LOH) and microsatellite instability [4]. Among the chromosomal anomalies, LOH at chromosome 1p is seen in early and well differentiated HCC and LOH at chromosomes 16p and 17p are seen in advanced HCC, implicating that deregulation of p53 is a major contributor for poor prognosis in HCC as in many other tumors. As a matter of fact, abnormality of p53 gene is noted in upto 60% of advanced tumors [4, 10]. In addition, there has also been reported familial cases with abnormalities in over expression of apolipoproteins family and serum amyloid A protein as possible genetic causes of HCC [11]. But genetic testing has not been done in our patients citing financial issues by the patient.

The clinical features and physical examination of a patient with familial HCC is not different from the one seen in patients with denovo cases. Majority of them are diagnosed when screened for unexplained asthenia, loss of weight, vague abdominal pain or a mass. The difference comes in terms of age of presentation. The familial cases invariably present at a much younger age. And in patients with the genetic aberrations mentioned, above tend to present with advanced disease. This fact is also seen in our report with one sibling presenting with incurable disease at 18 years of age and the other with a potentially resectable tumor [12]. This clearly indicates a genetic component and emphasizes the need for further testing to screen family members and also to test positivity for core antigen of HBV to include HBV as a potential cause but the testing has been negative in both our patients.

The diagnosis of HCC is made with a combination of imaging findings and elevated AFP levels. It has been known that AFP is elevated only in 50-60% of cases with HCC [12]. In Histopathology, these tumors stain positively for Hepar 1 and Glypican 3 markers and are negative for CK17 and CD34 [13] which was also seen in our patients. Also, both the subjects in the report had an elevated level of AFP and had typical features of HCC on imaging with an arterially enhancing lesion with early washout in the venous phase. The prognosis of HCC is provided by multiple staging systems of which the Barcelona Clinic Liver Cancer (BCLC) is widely followed [14]. As per BCLC, one patient was in stage A and underwent resection and the other patient was in Stage C and has been put on chemotherapy with sunitinib. The overall survival (5-year) in patients with stage A HCC is 40-70% and in advanced stages like stage C, the survival is less than a year. The subjects in the present report are on follow up to look into how the disease behaves and to detect early recurrences, if any.

Conclusion

The above case report is just the second case of familial HCC reported from our country as concluded by our extensive search in Pubmed Central but we feel that there is an element of under reporting that needs to be considered. We feel that genetic testing should be offered to these patient families to identify potential patients and a screening program be implied in areas with a high incidence of HCC. This is especially true in HBV endemic areas. We also feel that establishing a registry of familial cases and a set protocol of how to deal with them will help the clinicians to avoid any possible lacunae in treatment.

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