Case Report

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Disappearing Boundaries in Immunological Spectrum of Hepatocellular Carcinomas

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Abstract

Hepatocellular carcinoma (HCC) is an extremely rare tumour during pregnancy. HCC during pregnancy has a poor outcome and 20% of patients have distant metastasis at presentation according to previous reports. Malignancies should be carefully approached and considered as differential diagnoses in pregnant women. We present a case of a pregnant female with HCC associated with hepatitis B infection expressing biliary immunophenotype. Hepatocellular carcinoma (HCC) is an important, rare entity during pregnancy.

Keywords: Liver tumor; HepPar1; CK7; CK19; Cholangiocarcinoma

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte. Hepatocellular carcinoma (HCC) is very rare during pregnancy and has a worse prognosis in pregnant women compared to those who are not pregnant. Hepatocellular carcinoma frequently arises in the setting of cirrhosis, appearing 20-30 years following the initial insult to the liver. 25% of patients have no history or risk factors for the development of cirrhosis. Those with a family history of cancer should be more closely worked up, even if they present with unusual manifestations. Here we present a case of a pregnant female with HCC associated with hepatitis B infection expressing biliary immunophenotype.

Case Report

A 34-year-old primigravida, with 7 months amenorrhea, presented with the complaints of abdominal pain and jaundice since 15 days. She was detected to be hepatitis B positive 6 years back and was on treatment since then. Liver function tests showed total bilirubin to be 5.8 mg/dl, direct bilirubin 4.7 mg/dl, alkaline phosphatase 355 IU/L, aspartate transaminase 120 IU/L and alanine transaminase 42 IU/L. Serum alpha-fetoprotein was 393 ng/ml.

Ultrasonography showed a tumor in the liver with multiple, smaller satellite lesions in the adjacent parenchyma. Five days after admission, she went into pre-term labour and delivered a child who died due to meconium aspiration syndrome. Thereafter, the levels of liver enzymes progressively worsened and the patient could not survive. Complete post mortem was done. At autopsy, a large, firm, grey white tumour (16 × 12 × 7.5 cm) was seen in the left lobe of liver with multiple satellite nodules. **(Figure 1A)** The adjacent liver was non cirrhotic. Rest of the organs appeared normal.

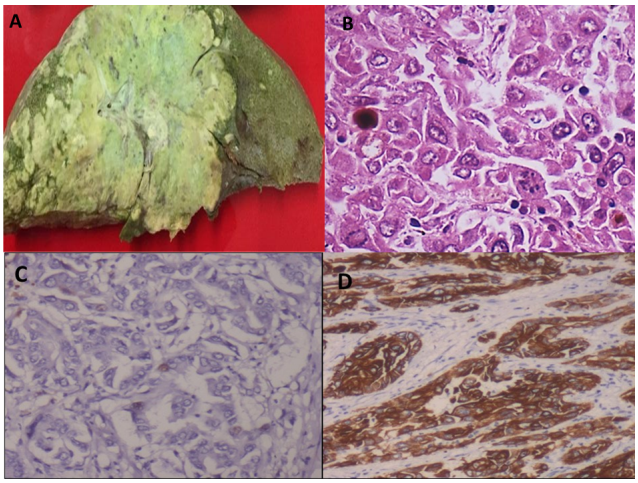

Figure 1: (A). Gross slice of liver showing tumor; (B). Tumor cells in trabecular pattern with bile production and abnormal mitosis (400x HE); (C). Tumor cells negative for Hep Par 1 (400x); (D). Tumor cells showing strong positivity with CK 7 (400x)

Histopathological examination of the tumor revealed moderately differentiated hepatocellular carcinoma. Tumor cells were arranged in trabecular and pseudo acinar patterns. Bile production was noted in some of the tumor cells. Abnormal mitosis was present. **(Figure 1B)**. Areas of extensive necrosis were present. Adjacent liver parenchyma was normal. There was no evidence of desmoplasia or mucin production. Immunohistochemistry was performed using hepatocellular markers HepPar1, Glypican-3 and polyclonal CEA (pCEA), all of which were negative within tumor cells **(Figure 1C)**. However,

adjacent liver parenchyma was positive for HepPar 1. Hence, another panel of antibodies CD34, CK7, CK19 and Ki67 was carried out. Tumor cells showed strong diffuse membranous positivity for CK7 **(Figure 1D)** and 19 while they were negative for CK20, CD117 and CD56. MIB1 index was 80%. This suggested that morphologically the tumor was HCC but immunohistochemically expressed biliary phenotype.

Discussion

Hepatocellular carcinoma is a rare tumor during pregnancy with very few cases reported in literature [1]. The tumor is aggressive with a lower survival rate as compared to non-pregnant females.

On light microscopic morphological evaluation, the present tumor was diagnosed as HCC. None of the sections were suggestive of cholangiocarcinoma. The unique feature was that in spite of classic HCC histomorphology, the tumor was negative for conventional hepatocytic markers (HepPar1, Glypican3 and pCEA) and strongly expressed biliary (CK7 and 19) immunophenotype. Hepatocytic markers are known to have low sensitivity to detect poorly differentiated HCCs. However, the present tumor showed moderate differentiation, with tumor cells resembling hepatocytes.

It has been established that hepatic progenitor cells, which are bipotential, can differentiate into hepatocytes or cholangiocytes [2]. These progenitor cells express CK7 and CK19 on immunohistochemistry. Several studies have reported prevalence of CK7 and CK19 expression in HCC (in addition to hepatocellular markers) to be 25% to 50% [3]. Such tumors have an aggressive course with poor survival [4]. The present case did not express hepatocyte markers but was positive for CK7 and 19. The possible hypothesis in this case may be the effect of pregnancy which has altered the immunophenotype or it may be the result of dedifferentiation of hepatocytes to biliary or progenitor cells during the process of tumor progression [5].

Conclusion

Cytokeratin7 and/or 19 positivity and lack of HepPar1 immunoreactivity on liver biopsy can lead to confusion and misinterpretation, not only for the pathologist but also for the clinician. Such patients may have to undergo further unnecessary investigations to rule out metastasis to the liver. We should be aware of such changing immunophenotypes of HCC which may predict poor clinical behavior.

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