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# Hepatocellular carcinoma arising in association with von-Meyenburg's complexes: an incidental finding or precursor lesions? A clinicopatholigic study of 4 cases

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**Abstract** Biliary hamartomas or von-Meyenburg complexes form part of a spectrum of ductal plate malformation that includes polycystic liver disease, congenital hepatic fibrosis, and Caroli disease. These lesions are known to have neoplastic transformation. Development of intrahepatic cholangiocarcinoma is well described in these complexes. Rarely, hepatocellular carcinomas (HCCs) have been seen in association with bile duct hamartomas, however; it is not clear whether development of HCC is an epiphenomenon unrelated to the precursor lesion or biliary hamartomas may progress to liver cancers. We herein report 4 interesting cases of hepatitis C virus–, alcohol-, and nonalcoholic fatty liver disease–associated end-stage liver disease with coexisting HCC and multiple large von-Meyenburg complexes.


*Keywords:* Biliary hamartomas; von-Meyenburg complexes; Hepatocellular carcinomas

## 1. Introduction

Bile duct hamartoma, also termed *von-Meyenburg complex* (vMCs), is a type of ductal plate malformation. This is a rare asymptomatic benign malformation of the intrahepatic bile ducts [1]. Neoplastic progression of vMCs is clearly described in the literature. These have been postulated to be the origin of cholangiocarcinoma (CCA) [2], although hepatocellular carcinomas (HCCs) [3], adenocarcinoid of the liver [4], as well as neuroendocrine carcinoma of the pancreas [5] in association with bile duct hamartomas have been reported. There are now 18 case reports and series that link CCA to a background of multiple vMCs [6]. However, association with HCC is rarely described; and it is not clear whether it is a direct cause-effect relationship. We describe 4 cases of hepatitis c virus (HCV)– and alcohol-induced cirrhosis with associated HCC and multiple vMCs. Because development of HCC and CCA has been described in the setting of hepatitis B virus (HBV) and HCV infections and alcohol-related liver disease, we hypothesize that HCC may develop because of neoplastic progression of vMCs.

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## 2. Case history

### 2.1. Case 1

A 55-year-old male patient presented in June 2006 for painful abdomen, loose stools, fever, and bleeding per rectum for 6 months. He was detected to have increased titers of HCV RNA of more than 700,000 IU/mL. There were no features of hepatic encephalopathy or ascites. He was diagnosed with HCV-related chronic liver disease (CLD) with HCC. The Model for End-Stage Liver Disease score and Child-Pugh class were 19 and B, respectively. Living donor liver transplantation (LDLT) was done in August 2006, and explant was submitted for histopathology.

### 2.2. Case 2

The second case involved a 59-year-old HCV-positive male patient transplanted for end-stage liver disease.

### 2.3. Case 3

A 60-year-old male chronic alcoholic patient was admitted for abdominal distension and upper gastrointestinal bleed in March 2006. Ultrasound of the abdomen revealed features of CLD, portal hypertension, and ascites.

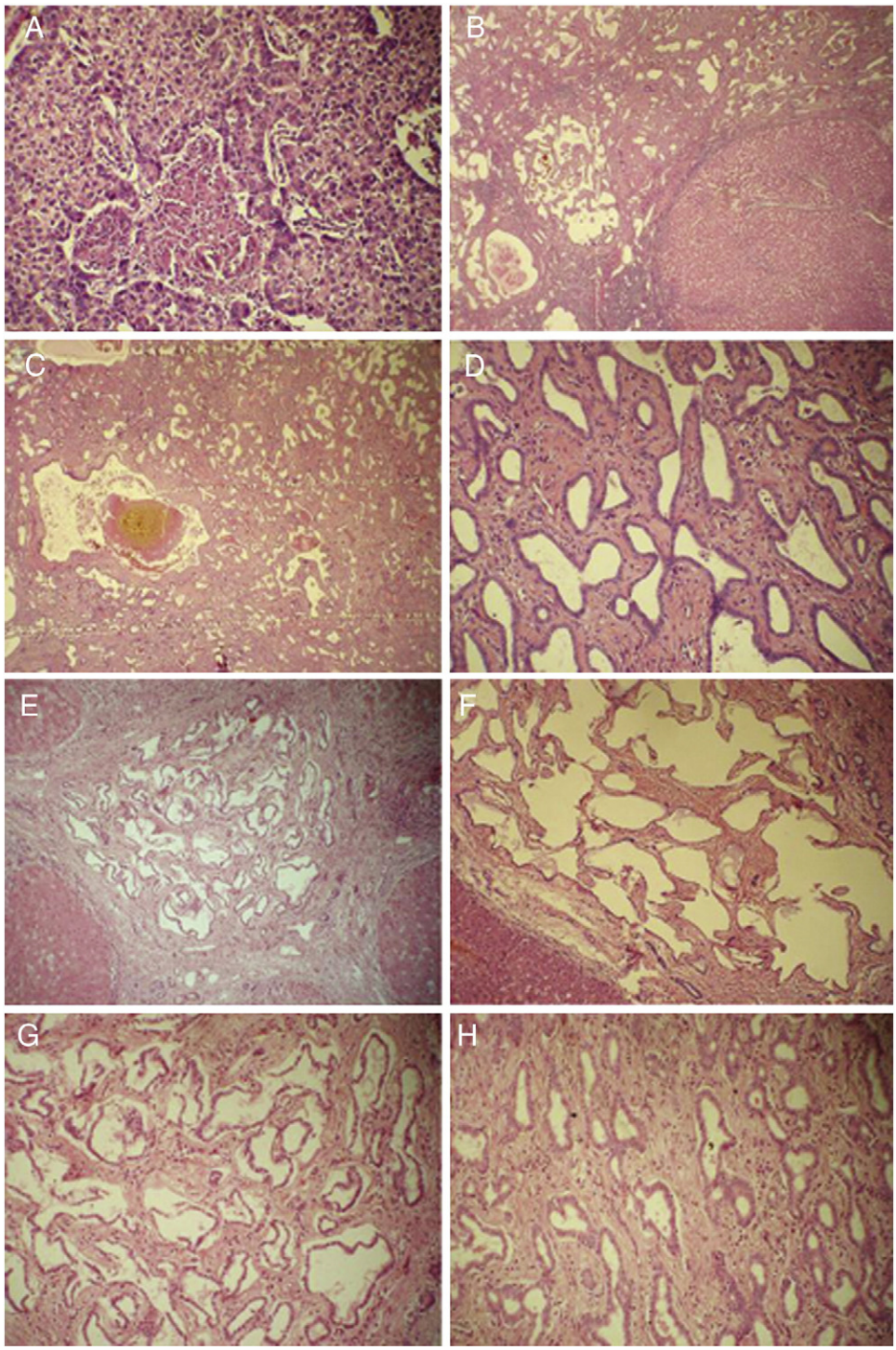


Fig. 1. Case 1. Photomicrograph shows moderately differentiated HCC with central necrosis (A, hematoxylin and eosin stain [H&E]; magnification ×400) and cirrhotic nodule with adjoining irregularly dilated biliary channels, some of which are filled with inspissated bile (B and C, H&E stain; magnification ×40 and ×100). Lining epithelium is simple cuboidal type (D, H&E; magnification ×400). E-H: Case 3. The proliferating bile channels were irregularly dilated and embedded in dense fibrotic stroma (E, H&E; magnification ×40; F-H, H&E; magnification ×400).

Upper gastrointestinal bleed endoscopy showed esophageal varices and severe portal gastropathy. In May 2007, the patient was readmitted with grade 3 hepatic encephalopathy and altered sensorium for 7 days. The LDLT was done with the clinical diagnosis of ethanol-related CLD and HCC. The Model for End-Stage Liver Disease score was 18, and Child class was C. The explant was submitted for histopathology.

### 2.4. Case 4

A 56-year-old male patient was diagnosed as a case of cryptogenic cirrhosis clinically. He underwent LDLT for decompensated state.

### 2.5. Gross pathology

Explant liver in cases 1 and 2 weighed 1420 and 1020 g, respectively. Outer and cut surface was nodular, with nodules varying in size from 0.2 to 0.5 cm. Cases 3 and 4 consisted of hepatectomy that weighed 1025 and 940 g, respectively. Tumor was located in the right lobe. Surrounding liver was cirrhotic and micronodular. Resection margins were free of tumor in all cases.

### 2.6. Histopathology

Microscopy from largest nodules showed a well- to moderately differentiated HCC (Fig. 1A). The rest of the liver in all cases displayed cirrhotic parenchyma with numerous proliferating bile ductules (Fig. 1B-H). The proliferating channels were irregularly dilated with or without luminal bile, signifying vMC. Lining epithelium was flattened and attenuated to simple cuboidal type. These ductules were embedded in dense fibrotic stroma. There was no transition seen between vMC and HCC.

## 3. Discussion

Biliary hamartomas are mainly incidental findings at laparotomy and autopsy [1]. Although malignant tumors that develop in the background of vMC are usually a CC, HCCs have also been reported (Table 1). Kim et al [7] reported a patient in whom HCC and CC arose separately in multiple vMCs. There was no evidence of direct contact or histologic transition between HCC and CC, and only the CC had a transition area from the vMC. A patient described in the series of Song et al [10] had combined HCC and CC, with the CC in the background of multiple vMCs and the HCC in a high-grade dysplastic nodule. However, Jain et al [8] found a focus of well-differentiated HCC as an incidental finding associated with multiple vMCs. In the present report, patients were proven cases of HCV, nonalcoholic fatty liver disease (NAFLD), and alcoholic cirrhosis, for which they had undergone LDLT. There were definite areas of mixed micromacronodular cirrhosis and multifocal well- to moderately differentiated HCC. In the cirrhotic parenchyma, there were numerous biliary hamartomas at places where the abnormal channels were filled with inspissated bile. In reviewing the literature, it is apparent that all cases except two [3] were associated with either viral hepatitis or other etiologic factors such as alcohol and hemochromatosis. It may be argued that HCC in these patients might have developed because of underlying precancerous etiologic factor, and vMCs are just incidental. However, the recently reported 2 cases by Heinke et al [3] do not have any causative agent. Moreover, there was no background cirrhosis. Now, it is a matter of debate whether vMCs are truly precursors of HCC or these are just an incidental finding. It needs to be explored in the future with further studies. Another issue to be discussed herein is the nature of vMCs, that is, whether they are always hereditary or may be a manifestation of marked bile ductular proliferation in end-stage cirrhotic livers. It has been noticed by Abraham and Torbenson [11] that vMCs may occur outside the setting of congenital hepatic fibrosis or polycystic liver disease and may be considered acquired lesions that increase with age and are associated specifically with cirrhotic-stage liver disease due to alcohol, HBV, and HCV/alcohol. More studies are however needed for further exploration of these lesions and their neoplastic nature.

Table 1
Reported cases of HCC associated with vMCs

| Author/year | Age/sex | Size (cm) | Location | No. of lesions | Associated disease | vMC | Histology | FU |
|---|---|---|---|---|---|---|---|---|
| Kim et al, 1999 [7] | 74/M | 4 × 5 and 2 × 2 | NA | 2 | HBV | Multiple | HCC, CC with cirrhosis | Alive at 2.5 y |
| Jain et al, 2000 [8] | 63/M | 1.5 | Left lobe | 1 | Alcohol | Multiple | HCC, CC | Died at 1 y |
| Blanc et al, 2000 [9] | 61/M | 2 and 4 | Right lobe | 2 | Hemochromatosis | Multiple | Moderately differentiated HCC,CC | NA |
| Song et al, 2008 [10] | 75/M | 4.5 | Right lobe | 1 | HCV | Multiple | HCC, CC with cirrhosis | Alive at 10 mo |
| Heinke et al, 2008 [3] | 19/F | Largest, 20.5 | Right lobe | Multiple | None | Multiple | Well-differentiated HCC | NA |
| Heinke et al, 2008 [3] | 39/M | 3.2 | Right lobe | Single | None | Multiple | Moderately differentiated HCC | NA |
| Present cases, 2010 | 55/M | 3.5 | Right lobe | Two | HCV | Multiple | Well to Moderately differentiated HCC | Well after 4 years |
| | 59/M | 3, 2.2, and 2 | Right lobe | 3 | HCV | Multiple | Moderately differentiated HCC | Well after 3 y |
| | 60/M | 3.5 | Right lobe | 1 | Alcohol | Multiple | Moderately differentiated HCC | Well after 3 y |
| | 56/M | 1 | Right lobe | 2 | NAFLD | Multiple | Moderately differentiated HCC | Well after 4 y |

F indicates female; M, male; NA, not available.

## 4. Conclusion

Our report adds 4 cases to the literature of vMC associated with HCC in the background of HCV-, alcohol-, and NAFLD-induced cirrhosis. However, molecular studies are needed to confirm and consolidate these associations.

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