Human Pathology (2017) **67**, 217–224

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Human PATHOLOGY

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Original contribution

Histopathological evidence of neoplastic progression of von Meyenburg complex to intrahepatic cholangiocarcinoma☆

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Received 8 May 2017; revised 4 August 2017; accepted 10 August 2017

Keywords:
Von Meyenburg complex;
Liver;
Intrahepatic cholangiocarcinoma;
Carcinogenesis;
Ki67;
p53

Summary Von Meyenburg complex (VMC) is generally thought to be benign, although its preneoplastic potential for intrahepatic cholangiocarcinoma (iCC) has been a subject of contention. We retrospectively reviewed 86 hepatectomy specimens with a diagnosis of iCC. Morphologically, an association between iCC and VMC was appreciated in 35% of cases that illustrated a gradual neoplastic progression from benign VMC to dysplasia and then to iCC. Among them, 24 cases had VMC lined by epithelial cells with low-grade biliary dysplasia and 13 with high-grade biliary dysplasia. VMC-associated iCCs were smaller in size and well to moderately differentiated, with features of anastomosing glandular architecture, ductal carcinoma in situ–like growth pattern, peritumoral lymphocytic infiltrate, central fibrous scar, and complete pushing border. They often presented as T1 tumors. In contrast, non–VMC-associated iCCs were moderately to poorly differentiated with solid, cribriform or papillary growth patterns. They likely exhibited necrosis, perineural invasion, positive surgical margin, lymphovascular invasion, and high T stage. Additionally, Ki67 and p53 immunostains support the continuing neoplastic evolution from benign VMC to dysplasia and then to iCC. VMC could become neoplastic, serving as an in situ carcinoma lesion to transform to iCC. The underlying molecular alteration and clinical implication of this neoplastic transformation deserves further investigation.

1. Introduction

Cholangiocarcinoma, a biliary tract malignancy, is the second most common primary hepatic cancer after hepatocellular carcinoma. Based on anatomic location, it is further classified into intrahepatic, perihilar and extrahepatic cholangiocarcinoma [1]. Intrahepatic cholangiocarcinoma (iCC) has been presumed to originate from hepatic progenitor cells within canals of Hering, peribiliary glands, dysplastic or immature cholangiocytes [2]. The incidence and mortality of iCC have been reported to be on the rise in USA [1]. The associated risk factors for iCC include cirrhosis, alcoholic liver disease, hepatitis C virus infection, diabetes mellitus, hepatolithiasis, chronic biliary disease and parasitic infestations inclusive of *Opisthorchis viverrini* and *Clonorchis sinensis* [3].

Von Meyenburg complex (VMC) that was first described in 1906 as a congenital cystic lesion, [4] is often found

☆ Disclosures: None.

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http://dx.doi.org/10.1016/j.humpath.2017.08.004
0046-8177/

incidentally and occurs in 5.6% of adult autopsies [5]. It is usually less than 5 mm in size and consists of benign bile ducts with irregular shape and dilated branches containing proteinaceous or bile-stained secretions in a background of dense fibrous stroma (Fig. 1A) [6]. Considered as a form of ductal plate malformation, VMC is also thought to be a microhamartoma that falls within the spectrum of fibrocystic liver disease.

VMC is generally thought to be benign. Although rare studies debated the association between VMC and iCC [7-10], the neoplastic progression from VMC to iCC is largely unknown. In this report, we studied the clinicopathologic features of iCC in a tertiary medical center with a large volume of hepatectomies. We aimed to evaluate whether there is an association between VMC and iCC. In combination with morphology, immunological markers were also used to explore the neoplastic progression from benign VMC to dysplasia and iCC.

2. Materials and methods

2.1. Patients

In this retrospective study, 86 patients who had a diagnosis of iCC were identified from Indiana University Health between 2002 and 2015. Clinical information regarding patients' age, gender, radiology reports, liver disease, and prognosis was extracted from the medical charts. The study was approved by the Institutional Review Board.

All cases were liver resections, and the hematoxylin and eosin–stained slides were reviewed by two pathologists (A.B. and J.L.). The pathologic diagnosis of iCC was confirmed in all cases according to the World Health Organization classification guidelines [3]. All the tumors in the study were mass-forming and were grossly examined according to the

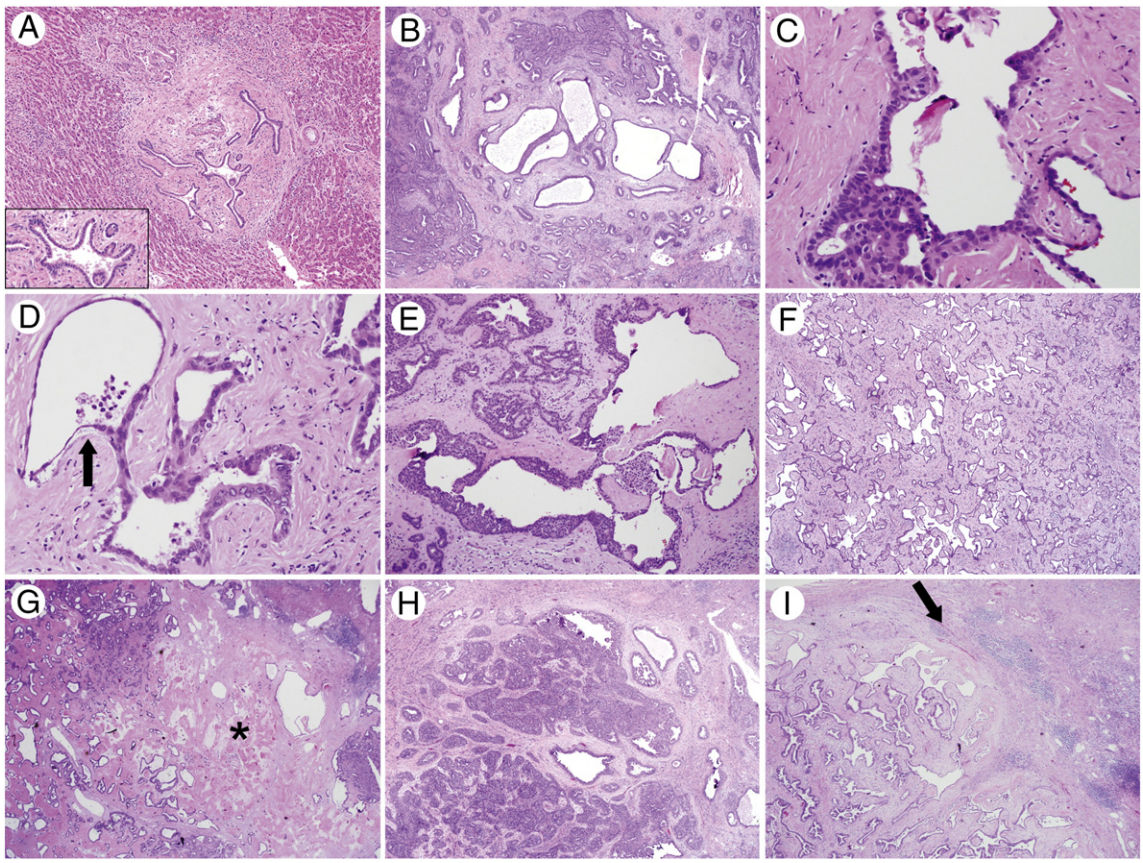

Fig. 1 Von Meyenburg complex (VMC) and associated intrahepatic cholangiocarcinoma. A, VMC is characterized by clusters of variably sized ductal structures with dilated lumina that are embedded in hyalinized fibrous stroma (×200). Inset: The irregular ducts are lined by benign flat and cuboidal epithelium (×400). B, A well-differentiated cholangiocarcinoma with associated VMC in the center (×40). C, VMC with low-grade biliary dysplasia, morphologically identical to biliary intraepithelial neoplasia 1 (×400). D, VMC with flat epithelia showing high-grade biliary dysplasia (×400). The arrow indicates the abrupt morphological transition from benign to dysplastic. E, VMC with high-grade dysplasia showing a pattern of micropapillary proliferation mimicking ductal carcinoma in situ (DCIS) of the breast (×400). F, Low-magnification view of a VMC-associated cholangiocarcinoma showing a unique pattern that recapitulates the architecture of VMC with a gradually worse differentiation component at the periphery (right side) (×40). G, Low-magnification review of a central fibrous scar lesion (*) that is surrounded by numerous neoplastic anastomosing and tubular glands (×40). H, Low-magnification view of a VMC-associated cholangiocarcinoma with a DCIS-like growth pattern (×40). I, Pushing border (arrow) with peritumoral lymphocytic infiltrate at the edge of a VMC-associated cholangiocarcinoma (×100).