CASE REPORT

Intrahepatic cholangiocarcinoma and portal hypertension developing in a patient with multicystic biliary microhamartomas

Toshitaka SUGAWARA[1], Junichi SHINDOH[1], Daisuke HOSHI[2], Masaji HASHIMOTO[1]

[1]*Hepatobiliary-pancreatic Surgery Division, Department of Digestive Surgery, Toranomon Hospital, Tokyo, Japan and* [2]*Department of Pathology, Toranomon Hospital, Tokyo, Japan.*

Abstract

Introduction: We report a case of intrahepatic cholangiocarcinoma and portal hypertension developing in a liver with biliary microhamartomas (von Meyenburg's complex). *Case Report:* The patient was a 55-year-old man who had a past medical history of diffuse multiple liver abscesses. During follow-up examination, a hypovascular nodule measuring 2.1 cm in diameter was incidentally found in segment 8 of the liver. Surgical resection was performed based on a suspected diagnosis of hepatocellular carcinoma. A gastrofiberscopy examination detected characteristic findings of portal hypertensive gastropathy. During the laparotomy, multiple tiny cystic lesions were observed in a diffuse pattern across the liver surface. The liver parenchyma was slightly fibrotic and haemorrhagic. A histopathological examination revealed intrahepatic cholangiocarcinoma with vascular invasions in von Meyenburg's complex. Multiple biliary adenomas were also observed among the biliary microhamartomas adjacent to the main tumour, suggesting that the malignant transformation of the biliary adenomas might have been responsible for the development of the intrahepatic cholangiocarcinoma. The histopathologic examination also revealed sinusoidal dilation and abnormal spacing of the portal tracts and central veins as evidence of portal hypertension.

Keywords: Biliary microhamartomas, von Meyenburg's complex, intrahepatic cholangiocarcinoma, portal hypertension

INTRODUCTION

Biliary microhamartoma was originally described in 1918 by von Meyenburg as a benign lesion and was subsequently named von Meyenburg's complex.[1] The reported incidence of biliary microhamartoma ranges from 0.5% to 5.6% in autopsy studies.[1,2] Biliary microhamartomas are typically asymptomatic and are detected incidentally during radiographic examinations in most cases. The size of the lesion usually ranges from 0.1 to 1.5 cm in diameter, and the lesions are observed diffusely over the whole liver. On magnetic resonance imaging (MRI), microhamartomas appear as hypo-intensities on T1-weighted images and as hyper-intensities on T2-weighted images.[3] To date, only a few studies have reported an association between von Meyenburg's complex and hepatic malignancies,[4,5] the majority of which were intrahepatic cholangiocarcinoma (ICC). Here, we report a case of ICC with portal hypertension

that developed in a liver presenting with von Meyenburg's complex and provide potential histopathological evidence of a malignant transformation from biliary adenoma to ICC.

CASE REPORT

A 55-year-old man had been referred to our department with fever and radiographic abnormalities three years previously. He had no significant past medical history. An abdominal MRI showed multiple tiny space-occupying lesions (Fig. 1A) presenting as hypo-intensities on T1-weighted images and as hyper-intensities on T2-weighted images. The patient was diagnosed as having multiple liver abscesses and was treated with antibiotics. After the successful resolution of his symptoms and inflammatory findings, however, the multiple cystic lesions in the liver persisted (Fig. 1B). During the follow-up period, a clear-margined nodule measuring 2.1 cm in diameter was detected using gadolinium-

Address for correspondence: Junichi Shindoh, MD, PhD, Hepatobiliary-pancreatic Surgery Division, Department of Digestive Surgery, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan. Tel: +81 03 3588 1111; Fax: +81 03 3582 7068. E-mail: shindou-tky@umin.ac.jp
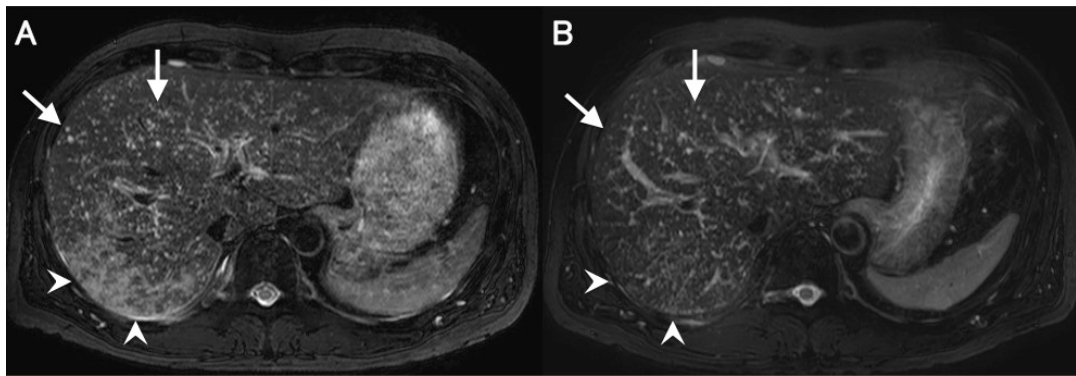
FIG. 1: Multiple liver microabscesses (arrowheads) and biliary microhamartomas (arrows) on T2-weighted magnetic resonance imaging. (A) Before treatment, (B) After treatment.

ethoxybenzyl-diethylenetriaminpentaacetic acid-enhanced MRI, presenting as a hypo-intensity on T1-weighted images and as a hyper-intensity on both T2-weighted images and diffusion-weighted images. The periphery of the nodule was enhanced during the arterial phase (Fig. 2A) and was visualised as a defect during the hepatobiliary phase (Fig. 2B). An abdominal enhanced computed tomography (CT) examination revealed an obscure lesion with unclear enhancement. An upper gastrointestinal endoscopy revealed portal hypertensive gastropathy. The alpha-fetoprotein, des-gamma carboxyprothrombin and carcinoembryonic antigen levels were within the normal limits, while a slight elevation in the carbohydrate antigen 19-9 level was observed (41 U/mL). Based on these findings, the patient was suspected of having ICC and surgical resection was scheduled. The indocyanine green retention rate at 15 minutes was 2.3%, and the Child-Pugh score was five.

During the laparotomy procedure, greyish-white nodules were observed in a diffuse pattern across the liver surface and the liver parenchyma was slightly fibrotic (Fig. 3A). Based on the location of the tumour, an anatomic resection of Segment 8 was performed (Fig. 3B). Although the hepatic functional reserve was normal, the liver parenchyma was firm and haemorrhagic during the parenchymal transection.

Histopathology
The pathological specimen revealed a solid, non-encapsulated, and polylobulated white nodule measuring 2.5 cm in diameter (Fig. 3C). The histopathological findings were compatible with features of ICC. Microscopic examination revealed diffuse microhamartomas (Fig. 4A) and dilated and irregularly angulated hyperplastic bile ducts (Fig. 4B) in the underlying liver parenchyma. The biliary epithelium exhibited polypoid growth, and bile-like materials were found inside the dilated bile ducts (Fig. 4C). These tiny biliary hamartomas were observed in a diffuse pattern on both lobes of the liver and were diagnosed as von Meyenburg's complex. In some parts of the biliary microhamartomas,
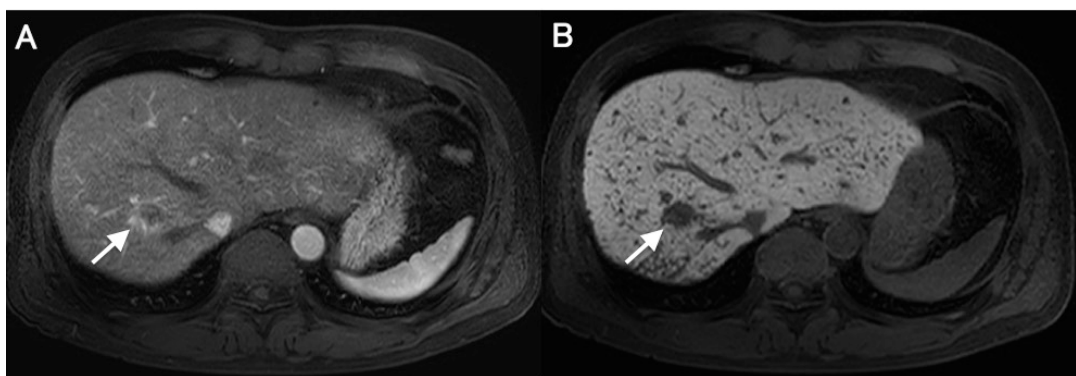

FIG. 2: Gadolinium-ethoxybenzyl-diethylenetriaminpentaacetic acid-enhanced magnetic resonance imaging showed a nodule in segment 8. (A) Arterial phase, (B) hepatobiliary phase.
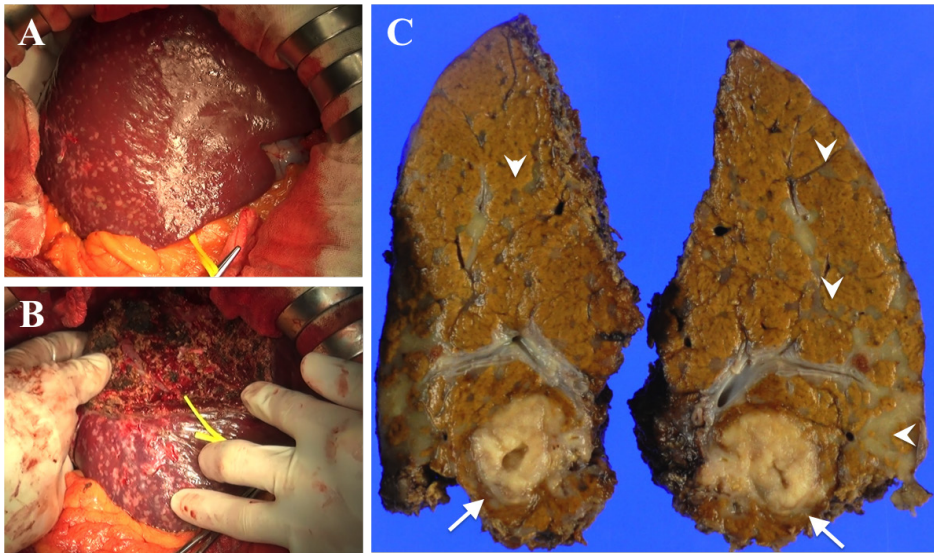
FIG. 3: Intraoperative photographs and the resected specimen. The liver was slightly fibrotic and presented with diffuse microhamartomas. (A) An anatomic resection of segment 8 was performed. (B) The pathologic specimen (C) revealed a white-gray, uncapsulated, multilobulated nodule (arrow). Diffuse biliary micro-hamartomas were visible within the liver (arrowhead).
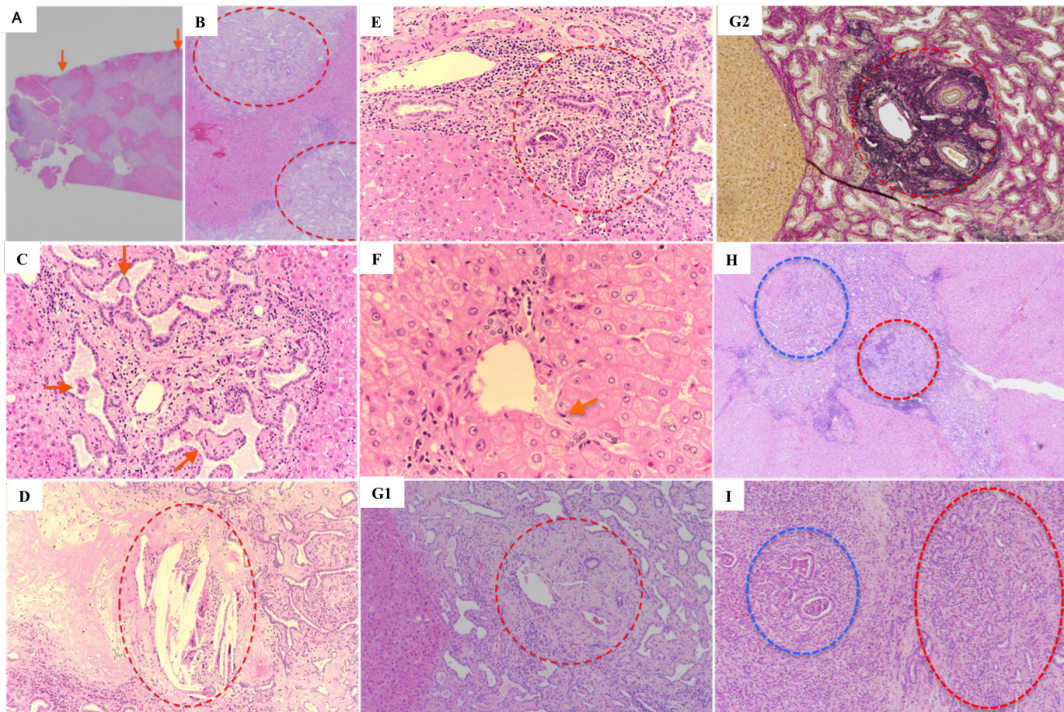

FIG. 4: Microscopic findings. (A) The biliary microhamartomas were numerous and confluent inside the liver parenchyma (arrow). (B) The bile ducts were hyperplastic, dilated and irregularly angulated (arrow). (C) Polypoid growth and bile-like materials were observed inside the dilated bile ducts (arrow). (D) Aggregation of multinucleated giant cells involving cholesterin crystals (dashed red line circle). (E) Inflammatory cell infiltration in the biliary microhamartomas (dashed red line circle). (F) Sinusoidal dilation (arrow). (G1) Narrowing of the portal vein caused by the biliary microhamartomas (dashed red line circle). (G2) Elastica van Gieson stain of G1. The portal vein was narrowed by hyperplastic collagen fibrils (pink) derived from the biliary microhamartomas (dashed red line circle). (H) Biliary adenomas (dashed blue line circle) among the biliary microhamartomas regions (dashed red line circle). (I) The main tumour (dashed blue line circle) among the biliary microhamartomas regions (dashed red line circle).

the aggregation of multinucleated giant cells involving cholesterol crystals, suggestive of a post-inflammatory reaction (Fig. 4D) or inflammatory cell infiltration (Fig. 4E), was observed. Additionally, slight to moderate sinusoidal dilation (Fig. 4F) and abnormal spacing of the portal tracts and central veins were observed as evidence of portal hypertension. The portal vein was narrowed because of hyperplastic collagen fibrils derived from the biliary microhamartomas (Fig. 4G). Biliary adenomas were scattered among the biliary microhamartomas (Fig. 4H), and the ICC component in the main tumour was adjacent to the adenoma regions, suggesting that the malignant transformation of a biliary adenoma might have occurred (Fig. 4I). Informed consent has been taken from the patient.

DISCUSSION

The aetiology of congenital bile duct disorder is the persistence or absence of remodelling of the embryonic ductal plate. This group of disorders includes Caroli's disease, autosomal polycystic kidney disease, congenital hepatic fibrosis, and von Meyenburg's complex.[6] Some studies have reported that ductal plate defects are associated with malignancies, with incidence of 1% in patients with congenital hepatic fibrosis and 7% in patients with Caroli's disease.[7] Mechanical or chemical irritation and chronic inflammation are also thought to be associated with carcinogenesis.[8]

In the present case, the history of liver abscesses and the state of chronic inflammation might have affected the malignant transformation from biliary adenoma to cholangiocarcinoma. To date, 22 patients with von Meyenburg's complex who developed ICC have been reported in English medical literature.[9,10] The median age of the reported cases was 68 years, 76% were male, and 95% of the patients presented with multiple biliary microhamartomas. The precise number and size of the biliary microhamartomas were not described. Song *et al.* reported a potential correlation between the size of biliary microhamartomas and the risk of malignant transformation.[9] Although it is difficult to validate this observation because of the rarity of such cases, the presence of persistent chronic inflammation, as confirmed in the current patient, might explain the malignant transformation based on the concept of the adenoma-carcinoma sequence.[11] Given the clinical and pathological evidence of chronic inflammation and the

microscopic findings suggestive of malignant transformation from biliary adenoma to cholangiocarcinoma, careful follow-up is likely to be needed for patients presenting with diffuse microhamartomas and infectious complications.

From a clinical standpoint, the underlying liver in the current case was firm and haemorrhagic, compared with a normal liver, although the underlying liver was not cirrhotic and the hepatic functional reserve was normal. Yoshida *et al.* reported a patient with severe portal hypertension caused by diffuse von Meyenburg's complexes.[12] They observed the displacement of the portal vein by dilated bile ducts and presumed that this displacement had caused the portal hypertension. Clinical evidence of portal hypertension was also confirmed during a gastrofiberscopy examination in the current case, and the histopathologic examination revealed sinusoidal dilation and abnormal spacing of the portal tracts and central veins as evidence of portal hypertension. The present observations suggest a correlation between diffuse microhamartomas and secondary portal hypertension, which could be associated with excessive bleeding and perioperative morbidity. Adequate care is required when clinical evidence of portal hypertension exists in a patient undergoing a hepatectomy.

CONCLUSION

In summary, although biliary microhamartoma is considered to be a benign disease, the associated histopathologic changes may cause portal hypertension and/or the malignant transformation of biliary adenomas because of chronic inflammation. Careful follow-up is needed, especially when diffuse microhamartomas are observed in patients with a history of infectious complications.

REFERENCES

1. Salo J, Bru C, Vilella A, *et al.* Bile-duct hamartomas presenting as multiple focal lesions on hepatic ultrasonography. Am J Gastroenterol. 1992; 87: 221-3.
2. Redston MS, Wanless IR. The hepatic von Meyenburg complex: Prevalence and association with hepatic and renal cysts among 2843 autopsies [corrected]. Mod Pathol. 1996; 9: 233-7.
3. Tohmé-Noun C, Cazals D, Noun R, *et al.* Multiple biliary hamartomas: Magnetic resonance features with histopathologic correlation. Eur Radiol. 2007; 18: 493-9.
4. Orii T, Ohkohchi N, Sasaki K, *et al.* Cholangiocarcinoma arising from preexisting biliary hamartoma of liver--Report of a case. Hepato-gastroenterology. 2003; 50: 333-6.

5. Heinke T, Pellacani LB, Costa Hde O, *et al*. Hepatocellular carcinoma in association with bile duct hamartomas: Report on 2 cases and review of the literature. Ann Diagn Pathol. 2008; 12: 208-2.

6. Desmet VJ. Congenital diseases of intrahepatic bile ducts: Variations on the theme "ductal plate malformation". Hepatology. 1992; 16: 1069-83.

7. Summerfield JA, Nagafuchi Y, Sherlock S, *et al*. Hepatobiliary fibropolycystic diseases. A clinical and histological review of 51 patients. J Hepatol. 1986; 2: 141-56.

8. Holzinger F, Z'Graggen K, Buchler MW. Mechanisms of biliary carcinogenesis: A pathogenetic multi-stage cascade towards cholangiocarcinoma. Ann Oncol. 1999; 10: 122-6.

9. Song JS, Lee YJ, Kim KW, *et al*. Cholangiocarcinoma arising in von Meyenburg complexes: Report of four cases. Pathol Int. 2008; 58: 503-12.

10. Xu AM, Xian ZH, Zhang SH, Chen XF. Intrahepatic cholangiocarcinoma arising in multiple bile duct hamartomas: Report of two cases and review of the literature. Eur J Gastroenterol Hepatol. 2009; 21(5): 580-4.

11. Fava G, Lorenzini I. Molecular pathogenesis of cholangiocarcinoma. Int J Hepatol. 2012; 2012: 630543.

12. Yoshida S, Kurokohchi K, Ueno T, Yoshino M, Shimada M, Masaki T. Hepatic von Meyenburg complex: a trigger of severe portal hypertension. Liver Int. 2009; 29(4): 614-5.