



## Biliary intraepithelial neoplasia in liver parenchyma of the caudate lobe: honeycomb appearance

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### Summary

**Background** Biliary intraepithelial neoplasia (BilIN) was newly defined by the WHO in 2010 and is characterized by biliary cell atypia with an intraductal papillary lesion. It is always found in the major bile duct, but not in liver parenchyma.

**Case presentation** A 50-mm irregular tumor was detected in the paracaval portion of the hepatic caudate lobe of a 61-year-old man. He had undergone total gastrectomy for advanced gastric cancer 2 years earlier. The tumor had increased from 20 to 50 mm in the last 6 months. Abdominal CT showed an irregular hypo-enhanced tumor, with a honeycomb appearance inside the tumor. Diffusion-weighted MRI and PET showed that the tumor had malignant features, though no tumor markers were elevated. The tumor seemed to invade into the inferior vena cava (IVC) and hepatic veins. At operation, under side clamping of the IVC, a total of 10 cm of ventral side IVC was resected with the left liver. Pathologically, the tumor was an inflammatory pseudo-tumor that contained intermediate-grade BilIN of persistent liver parenchyma in the tumor.

**Conclusion** The honeycomb appearance within the tumor showed a causal relationship between the

pathological and etiological representations of BilIN. Considering BilIN avoids an unnecessary operation when we encounter atypical imaging findings of liver tumors.

**Keywords** Biliary intraepithelial neoplasia · Honeycomb appearance · Concomitant IVC resection · Caudate lobe tumor

### Abbreviations

BilIN Biliary intraepithelial neoplasia  
 DWI Diffusion-weighted imaging  
 PET Positron-emission tomography

### Introduction

The concept of biliary intraepithelial neoplasia BilIN was established in 2005, and a consensus was reached on the terminology in 2007 [1, 2]. In the 2010 revision of the WHO classification of tumors, BilIN and IPNB (intra-papillary neoplasm of bile duct) became distinct biliary tumors. The pathological difference between BilIN and IPNB is the morphological pattern and the presence of mucin production [2]. Morphologically, BilIN is defined by flat or micropapillary dysplasia in the biliary epithelial cells, while IPNB is defined by macropapillary lesions. The dysplasia is graded depending on the degree of dysplastic cells (BilIN-1, low-grade; BilIN-2, intermediate-grade; and BilIN-3, high-grade). BilIN-1 and 2 are found around inflammation sites of the major bile duct, while they are rarely found in the liver parenchyma. In contrast, BilIN-3 is observed as a peripheral lesion in approximately 70% of hilar cholangiocarcinomas [3, 4].

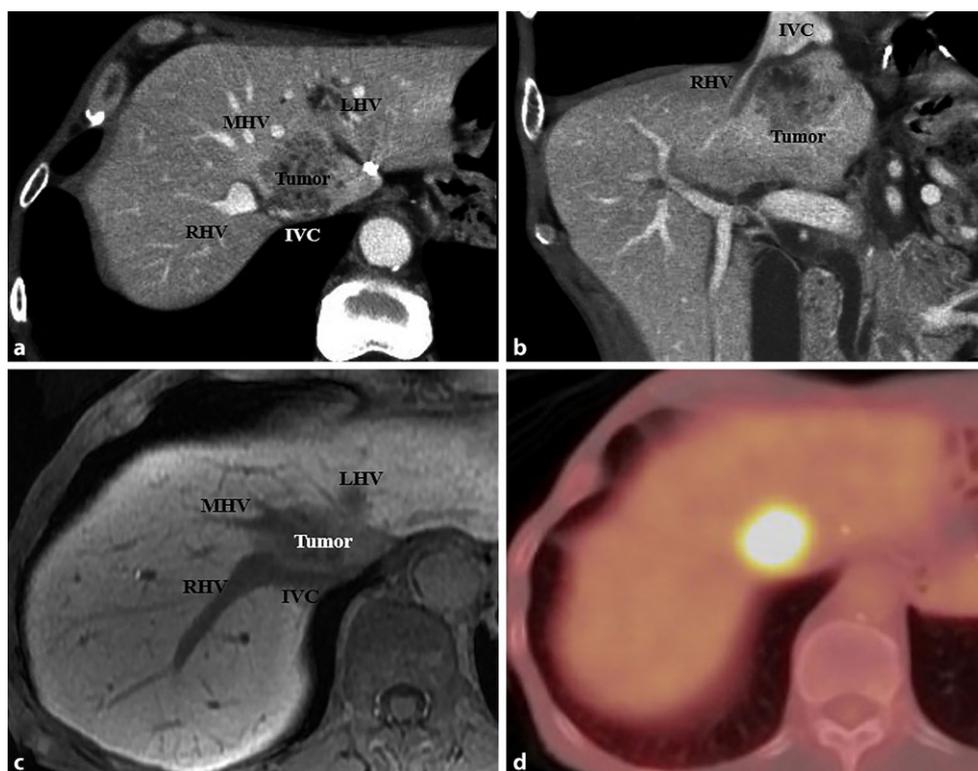
For the first time, a specific feature that suggests the presence of BilIN in liver parenchyma was identified. It shows a causal relationship between diagnostic and pathological images in the diagnosis of BilIN.

**Author contribution** T. Higaki collected patient data, S. Yamazaki wrote the manuscript, M. Sugitani advised on pathological data, and T. Takayama supervised the manuscript.

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**Fig. 1** Preoperative imaging study. Enhanced CT shows a hypo-enhanced irregular tumor that contains dots in the caudate lobe. The tumor is close to the inferior vena cava (IVC) and right hepatic vein (RHV), while it has invaded into the left (LHV) and middle (MHV) hepatic veins. (a, b) MRI shows a low-intensity tumor on the T1-weighted image, but the IVC and RHV are preserved on the T2-weighted image (c). The standardized uptake value of the tumor on positron-emission CT is 12.1 Bq/ml (d)



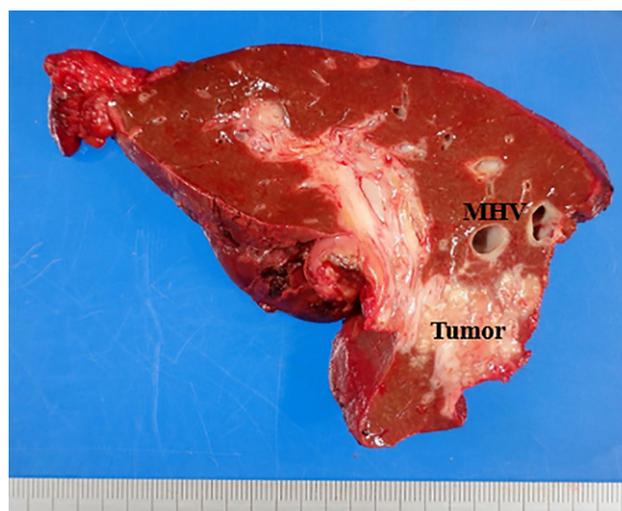
The diagnosis of BillIN can only be made after pathological examination. Most surgically treated cases are located not in the liver parenchyma, but in the major bile duct. Thus, no reports have described the specific diagnostic imaging features of BillIN preoperatively.

### Case presentation

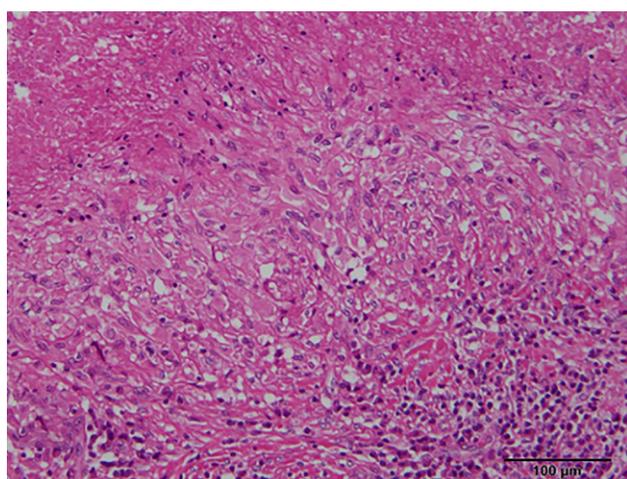
A 61-year-old man was admitted to undergo treatment for a 50-mm irregular tumor in the caudate lobe of the liver. He had a history of advanced gastric cancer and had undergone total gastrectomy 3 years earlier. The tumor was found during a follow-up examination, and it increased in size from 20 to 50 mm over a 6-month period. He had no history of viral hepatitis, biliary stones, or other chronic liver diseases. There were no elevations of any tumor markers, liver enzymes, or the inflammatory response during follow-up.

A hypo-enhanced, heterogeneous, irregular tumor with a dot structure within the tumor—presenting a honeycomb appearance—was observed in the caudate lobe on enhanced CT (Fig. 1a). The tumor seemed to invade into the inferior vena cava (IVC) and hepatic veins. The tumor showed low intensity on T1-weighted and high intensity on T2-weighted images (Fig. 1b, c). Based on diffusion-weighted MRI and the uptake pattern on positron-emission tomography (PET), the tumor was diagnosed to be a metastatic liver tumor or cholangiocellular carcinoma, and surgery was considered contraindicated in the previous institution (Fig. 1d). However, the tumor did not have the typical imaging findings of

liver malignancy, and there were no tumor marker elevations or other comorbidities. Thus, extended left lobectomy with partial resection of the IVC was planned. The preoperative diagnosis was liver metastasis from gastric cancer or cholangiocarcinoma, and



**Fig. 2** Macroscopic image of the tumor. A total length of 10 cm of the inferior vena cava has been resected with the left lobe of the liver. A 5-cm, irregular, solid, white-colored tumor (*Tumor*) is confirmed in the resected specimen. Multiple macroscopic small cysts are observed in the tumor, while there is no mucin production or papillary lesions within the cysts. *MHV* middle hepatic veins



**Fig. 3** Histopathological examination of the tumor. Marked inflammatory cell infiltrate in the liver parenchyma in the tumor. In the cystic lesions, intermediate-grade dysplastic biliary epithelial cells are found around the liver parenchyma. (Original magnification: × 20)

the honeycomb appearance within the tumor was considered hemorrhage.

At operation, the tumor seemed to have invaded widely to the IVC, middle hepatic vein, and left hepatic vein. Thus, a length of 10 cm of the ventral side of the IVC was resected under side clamping along with tumor (Fig. 2). Macroscopically, the tumor was an elastic solid white mass, with multiple small cystic lesions observed within the tumor. There was no mucin production, hemorrhage, or visible papillary lesions within the small cysts (Fig. 2). Histologically, massive inflammatory cells infiltrated to the liver parenchyma, and flat micropapillary neoplastic lesions were confirmed in the dilated bile ducts. Intermediate-grade cellular atypia and structural dysplasia were found in the biliary epithelium (Fig. 3).

The tumor was diagnosed as an inflammatory pseudo-tumor with intermediate-grade biliary intraepithelial neoplasia (BillIN-2) in the liver parenchyma. The patient's postoperative course was uncomplicated, and there were no signs of recurrence for 2 years after surgery.

## Discussion

The honeycomb appearance on preoperative imaging shows a causal relationship between the etiological and morphological representations of BillIN. These multiple small bile duct dilatations in the remnant liver parenchyma within the tumor might represent a specific feature of BillIN.

Most BillINs were easily found in the major bile duct as mass-forming lesions with bile duct dilatation [5–8]. In contrast, there have only been two previously reported cases of BillIN in the liver parenchyma since it was defined by the WHO [1, 2]. In the other two cases, BillIN was found after liver transplantation and inside an infected biliary cyst [9, 10]. This means that patients who have chronic parenchymal inflammation are at risk for BillIN. However, there were no episodes of inflammation in the present case.

Intermediate- to low-grade BillINs were found in chronic biliary diseases such as primary sclerosing cholangitis (PSC), Caroli disease, hereditary liver fibrosis, choledochal cysts, and biliary stones [4–10]. In contrast, BillIN-3 was observed as a peripheral lesion in approximately 70% of hilar cholangiocarcinomas [3]. However, the natural history and long-term follow-up data of BillIN are unknown. There was no significant difference in patients' survival between cases with or without BillIN in the surgical margin in cases of hilar cholangiocarcinoma [11]. Therefore, intermediate- to low-grade BillIN may not need immediate surgical treatment.

PET showed strong uptake because of the inflammation of the liver parenchyma. On the basis of the etiology, it makes sense that the dilated bile ducts reflect a honeycomb appearance within the tumor. Therefore, this appearance on CT and MRI has value for the diagnosis of BillIN. Liver abscess is one of the differential diagnoses, but there were no episodes of biliary inflammation. Thus, needle biopsy is a possible option, but it was ruled out because of the tumor's location and the possibility of cancer seeding.

The treatment strategy of BillIN is under debate. The surgical treatment cases are limited and there are no data on natural history. To our knowledge, this is the third surgical case of BillIN in the liver

**Table 1** Patients characteristics of biliary epithelial dysplasia in reported cases

Author	Year	Age	Gender	Clinical manifestation	Location	Treatment	Histological diagnosis
Aggarwal [5]	2003	55	M	Abdominal pain	CBD	PD	Adenoma with moderate dysplasia
Lou [6]	2003	47	M	Abdominal pain	CBD	Local excision	Tubular adenoma with moderate dysplasia
Katsinelos [7]	2006	58	M	Jaundice	CBD	PD	Villous adenoma with atypia
Xu [8]	2008	27	F	Jaundice	CBD	PD	Villous adenoma with mild dysplasia
Rougemont [9]	2010	42	M	Post liver transplantation	Liver	Liver resection	High-grade biliary intraepithelial neoplasm
Wang [12]	2016	77	M	Discomfort	CBD	Local excision	High-grade biliary intraepithelial neoplasm
Umemura [10]	2016	65	M	Liver cyst with inflammation	Liver	Liver resection	Middle-grade biliary intraepithelial neoplasm
Present case	2017	61	M	Incidental	Liver	Liver resection	Middle-grade biliary intraepithelial neoplasm

CBD Common bile duct, PD pancreatoduodenectomy

parenchyma; most of the cases were in the thick biliary duct ([5–10, 12]; Table 1). The previous two cases found in liver parenchyma were after liver transplantation and in a liver biliary cyst with inflammation. Thus, they had chronic parenchymal inflammation. In present case, BillN was found in the follow-up course of gastric cancer. There was no episode of biliary inflammation and no other background providing grounds to speculate BillN. Therefore, we could not reach an accurate diagnosis preoperatively.

The preoperative diagnosis of BillN is difficult because of its low incidence and few clinical manifestations. A honeycomb appearance on preoperative imaging suggests the possibility of BillN and may avoid unnecessary surgery.

#### Compliance with ethical guidelines

**Conflict of interest** T. Higaki, S. Yamazaki, M. Sugitani, and T. Takayama declare that they have no competing interests.

**Ethical standards** This article does not contain any studies with human participants or animals performed by any of the authors. The manuscript was approved by the Institutional Review Board of Nihon University School of Medicine.

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