Int J Clin Exp Pathol 2016;9(10):10036-10043
www.ijcep.com /ISSN:1936-2625/IJCEP0026640

Original Article

Intrahepatic cholangiocarcinoma arising from bile duct adenoma

Zhan-Bo Wang[1*], Yong Guo[2*], Jing Yuan[1], Po Zhao[1], Huai-Yin Shi[1]

[1]Department of Pathology, PLA General Hospital, Beijing, China; [2]Department of Pathology, 161 Hospital of PLA, Wuhan, Hubei, China. [*]Equal contributors.

Received February 25, 2016; Accepted May 21, 2016; Epub October 1, 2016; Published October 15, 2016

Abstract: Objective: Bile duct adenoma (BDA) is a very rare benign lesion of the bile duct. To improve diagnosis and the ability to predict prognosis, this study investigated the potential for malignant transformation of BDA in the liver, including a literature review. Methods: Four female patients with intrahepatic cholangiocarcinoma arising from BDA were clinicopathologically evaluated. Immunohistochemical examination was conducted with several antibodies using the EnVision+ system. The V600E mutation in *BRAF* was tested via RT-PCR. Relevant literature was reviewed. Results: The 4 patients presented with abdominal swelling and pain. Serum levels of CA199 (carbohydrate antigen 19-9), CEA (carcinoembryonic antigen), CA125 (cancer antigen 125), and AFP (alpha-fetoprotein) were within normal limits. Microscopy revealed tumors with many normal-looking bile ductules and scant-to-moderate surrounding connective tissue. The stroma showed mild inflammation with predominant lymphocytes. The ductule lumens were narrow or slightly dilated. Distinct irregular and atypically shaped bile ductules of different sizes were noted. There was a transitional zone from apparently benign-to-markedly atypical bile ductules. Mitotic figures were occasionally seen. In one patient, areas of cystically dilated ductules with brown bile plugs were observed, similar to the ductal plate malformation pattern. Immunohistochemical analyses showed positive staining for cytokeratin 19, mucin-6, and HER2 in the cholangiocarcinoma area. BDA lesions were NCAM1 (neural cell adhesion molecule 1 or CD56)-positive; cholangiocarcinomas were NCAM1-negative. V600E mutations were also identified in 2 patients. Conclusions: Cholangiocarcinoma can develop from BDAs. BDAs may be true neoplasms and may be suspected as early cholangiocarcinoma. Adenoma-to-carcinoma cholangiocarcinogenesis may be linked to *BRAF* mutation.

Keywords: Cholangiocarcinoma, adenoma, bile duct, *BRAF*

Introduction

Bile duct adenoma (BDA) is a rare form of benign bile duct lesion, and is usually symptomless. Most often, BDA has been stumbled upon via surgery or autopsy, on the surface of the liver. The mean diameter of BDAs is 5.8 mm, but range from 1 to 20 mm [1]. Occasionally, they may occur as multiple nodules in the liver [2]. Surgeons and pathologists may confuse BDA with metastatic adenocarcinoma, especially during surgery.

Morphologically, BDA is quite similar to bile duct hamartoma (BDH) [3], although in BDH lesions bile plugs are more common in the duct lumens. The few reports describing cholangiocarcinoma associated with BDH [4-6] suggest that BDH may be a precursor to intrahepatic cholangiocarcinoma (ICC). However, malignant transformation of BDA is rare.

Herein, we report 4 cases of BDA in which areas of atypical bile ductules and an invasive growth pattern were identified as ICC. In addition, we review the literature published in English over the past 30 years (1984-2015) of the pathological features of 5 cholangiocarcinomas arising from BDAs [7-11].

Methods

Four patients with BDA were admitted to Chinese PLA General Hospital between the years 1990 and 2014. Tumor tissue sections were retrieved from paraffin blocks of tissues collected for surgical pathology reports. Pathological diagnoses were made in accordance

Table 1. Cases of cholangiocarcinoma associated with BDA

First author, y	Gender	Age, y	Location	Size, cm	Single/multiple	Surgery	Follow-up
Börnfors, 1984	M	80	LL	0.5, 3	Multiple	Surgery	DOD, 10 y
Foucar, 1985	F	NA	NA	NA	Single	Biopsy	DOD, 15 y
Hasebe, 1995	M	59	LL	5.5	Single	Surgery	ANED, 19 mo
Pinho, 2012	F	60	RL	3.8	Single	Surgery	NA
Kwon, 2015	F	36	LL	2	Single	Surgery	ANED, 28 mo
Present case 1	F	52	LL	9	Single	Surgery	ANED, 36 mo
Present case 2	F	67	RL	5.0	Single	Surgery	ANED, 37 mo
Present case 3	F	59	LL	3.5	Single	Surgery	ANED, 6 mo
Present case 4	F	53	Caudate & LL	6.5, 0.8	Multiple	Surgery	DOD, 62 mo

ANED, alive with no evidence of disease; DOD, dead of disease; LL, left lobe; RL, right lobe; NA, not available.

with the World Health Organization Histologic Classification of Liver Tumors and Intrahepatic Bile Ducts [12].

Immunohistochemical staining of the tissues was performed using the Envision two-step method [13]. Briefly, formalin-fixed, paraffin wax-embedded, and 4-μm-thick sections were prepared as previously described [13]. The slides were incubated serially (40 min each, at room temperature) with the following primary antibodies: TP53 (1:100); MKI67 (1:100); cytokeratin-7 (CK7, 1:100); cytokeratin-19 (CK19, 1:100); cyclin D1 (CCND1; 1:100; Dako, Denmark); NCAM1 (CD56, 1:100; Gene Tech, Shanghai); HER2(1:300; Dako, Denmark); mucin-6 (MUC6; 1:100; Gene Tech, Shanghai).

Each incubation with primary antibody was followed by 40-min incubation at room temperature with horseradish peroxidase-labeled polymer. The staining was developed by incubation with diaminobenzidine substrate-chromogen for 5-10 min, and a hematoxylin counterstain was applied. Both negative and positive controls for each antibody were performed.

For HER2, more than 10% of tumor cells with complete membranous staining was considered positive [14]. For the other antibodies, immunoreactivity in more than 5% tumor cells was regarded as positive.

Genomic DNA was extracted from paraffin-embedded blocks with QIAGEN QIAamp. Samples were screened for *BRAF* (b-raf, serine/threonine kinase; codon 600) mutations by means of an ARMS-PCR Kit (Amoy Diagnostics, Xiamen, China). The whole process was conducted in accordance with the suggested methods [15].

Results

Clinical presentation

All 4 patients were women, aged 52, 67, 59, and 53 years (cases 1, 2, 3, and 4, respectively), with tumors located at the left, right, left, and caudate lobes of the liver (**Table 1**). Abdominal swelling and pain were common to all these patients.

Laboratory findings

Both the hepatitis B virus and hepatitis C virus serum markers were negative in all 4 cases. Serum levels of CA 19-9, CEA, CA-125, and AFP were all within normal range.

Imaging findings

The tumors in the livers of all patients were observed in ultrasound and CT scans of the abdomen. Magnetic resonance imaging revealed masses of heterogeneous hyper-signal intensity (**Figure 1A**).

Gross findings

Complete resection of the tumor was performed for all 4 patients. In case 1, one tumor nodule was identified in the left lobe (diameter 9 cm; **Figure 1B**). The tumor was clearly circumscribed from the surrounding parenchyma in the liver, yet without apparent capsule. The cut surface of the tumor was grayish-white, showing no foci of necrosis or hemorrhage.

In case 4, two tumor nodules were identified, with one in the caudate lobe (diameter 6.5 cm) and the other in the left lobe (diameter 0.8 cm). Only one tumor nodule was seen in each of cases 2 and 3, with diameters 5 cm and 3.5

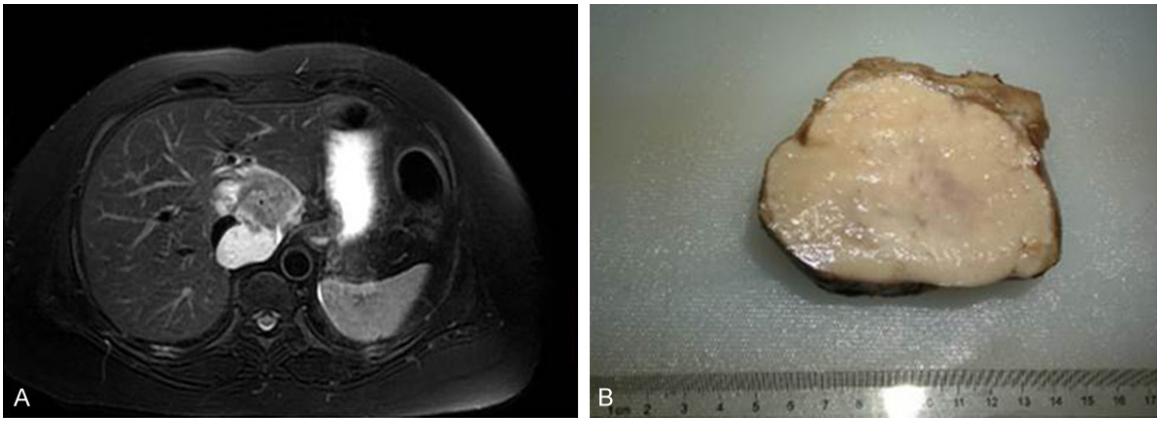

Figure 1. A. The fourth case: Magnetic resonance imaging of an inhomogeneous hyper-signal intensity mass in the caudal lobe of the liver. B. The first case: The cut surface of the specimen showing a solitary node located in the subcapsular region.

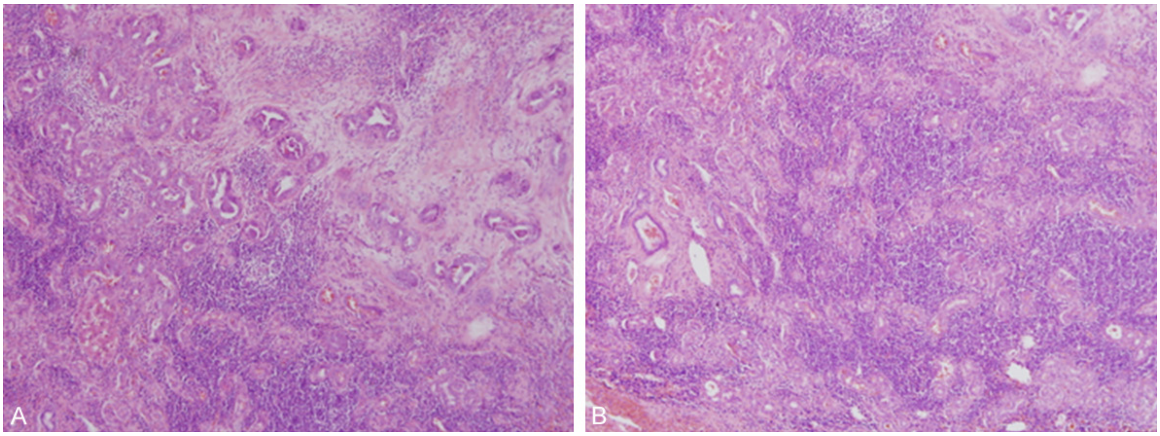

Figure 2. In all four cases, A. atypical bile ductules were observed adjacent to obvious benign ductules (right). Some of them invaded adjacent stroma (right). H&E, 200×. B. Highly packed bile ductules were observed in various amounts of surrounding connective tissue. The stroma showed mild inflammation, and the inflammatory cells were predominantly lymphocytes. H&E, 200×.

cm, respectively. These tumor nodules appeared grayish-white and were poorly delineated from the surrounding area.

Microscopic findings

The tumors were composed of many normal-looking bile ductules. The lumen of the ductules was narrow or slightly dilated. There was a scanty-to-moderate amount of connective tissue in the tumor area. Besides that, irregularly shaped and apparently atypical bile ductules of various sizes were observed, and some of them invaded the stroma and extended into the adjacent liver parenchyma. A transitional zone between the apparently benign bile ductules to markedly atypical bile ductules was present (**Figure 2A**). Mild inflammation with prominent lymphocytes in the stromal tissue were also noted (**Figure 2B**).

Regarding the tumor, there was a morphological area of transition from obvious benignity to apparent dysplasia, carcinoma *in situ* to invasive cancer. Epithelial cells of irregularly shaped ductules had atypical nuclei with coarse granular chromatin (**Figure 3A**). In addition, in case 4, an area of cystically dilated ductules with bile plugs was observed, which resembled a ductal plate malformation (DPM) pattern [11] (**Figure 3B**).

Immunohistochemical analysis

In all the 4 cases, the carcinomatous areas reacted similarly to CK7 and CK19, showing

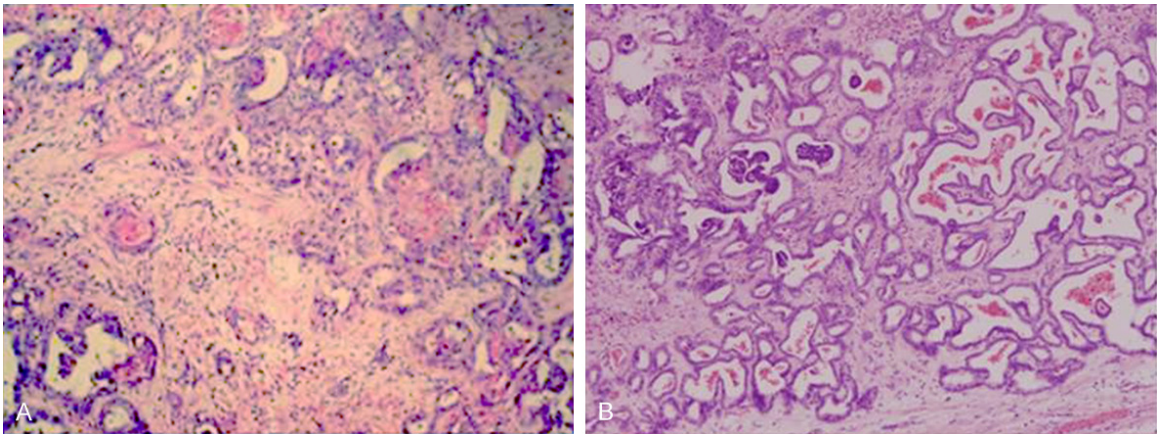

Figure 3. The fourth case. A. Epithelial cells of irregularly shaped ductules had atypical nuclei with coarse granular chromatin. H&E, 400×. B. Carcinoma with a DPM pattern that conformed to that of classical cholangiocarcinoma. H&E, 200×.

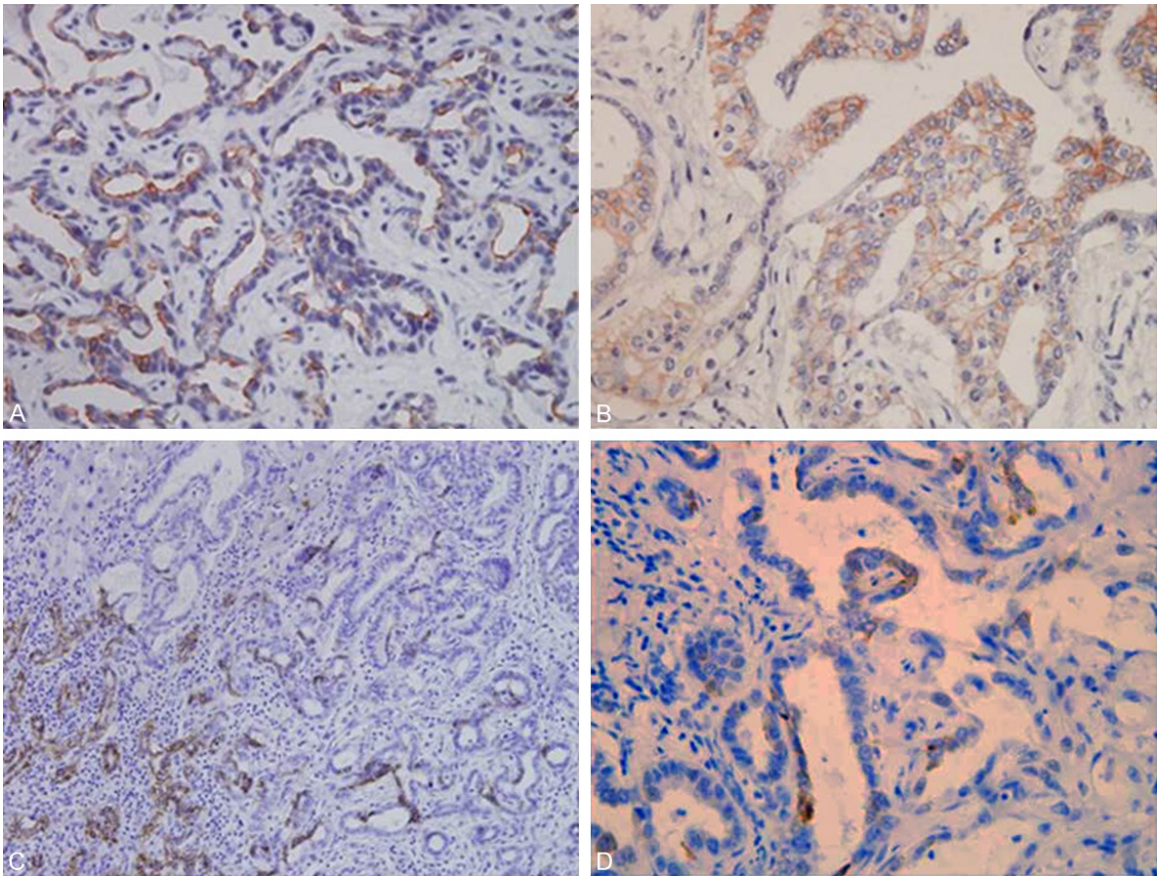

Figure 4. Immunohistochemical staining of cholangiocarcinoma in all four cases. A. Both benign bile ductules and carcinomatous areas show positive staining for CK19 (200×). B. Immunohistochemical staining for Her-2. Note continuity of the carcinomatous areas which stained strongly. H&E 400×. C. CD56 is strongly and diffusely apparent in the benign area, and negative in the malignant area (200×). D. Carcinomatous areas were positive for Muc-6 (400×).

positivity for CK7 and CK19 (**Figure 4A**) and were negative for CCND1. In contrast, ductules in the carcinomatous areas were positive for HER2 (**Figure 4B**), while the marker was nega-

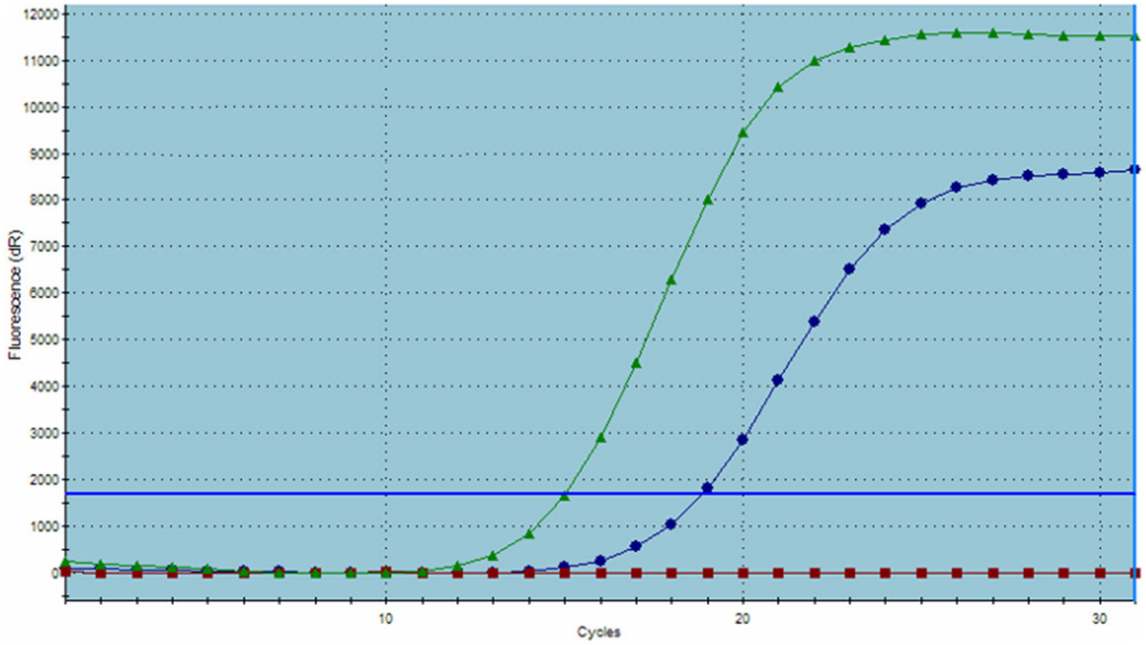

Figure 5. The third and fourth case. Amplification plot of tumors showing *BRAF* V600E mutation: mutated control sample (green curve) and mutated patient sample (blue curve), compared to a negative control sample (red curve).

tive or weakly positive in the BDA and DPM-like areas. In addition, BDAs were NCAM1-positive, whereas cholangiocarcinomas were NCAM1-negative (**Figure 4C**), and TP53 was focally positive in the malignant areas. The MKI67 labeling index was higher (10-15%) in the malignant areas. In all cases, MUC6 was positive in the carcinomatous area (**Figure 4D**).

BRAF V600E mutation analysis

The *BRAF* mutational status of all 4 cases was measured. The V600E mutation in *BRAF* was detected in 2 patients (50%; **Figure 5**).

No other primary tumors were detected in any of the 4 cases. Therefore, these neoplasms were diagnosed as ICC, arising from BDA.

Literature review regarding cholangiocarcinoma arising from BDA

Only 5 cases of cholangiocarcinoma associated with BDAs have been reported in the English literature [7-11] (**Table 1**). All the reported tumors occurred mainly in middle-aged and older people (mean age, 58.2 years) with a slight female predominance (77.8%). The overall 5-year survival rate was almost 100%, while the median survival rates were approximately 12.2 months for patients with classic ICC [16].

Discussion

BDA occurs most often as a single benign lesion located in the subcapsular region of the liver, and well circumscribed without a capsule [17]. Some authors claim that it is a reactive proliferation rather than neoplastic [18], whereas others believe that it is a true neoplasm [19] [20]. It may be a peribiliary gland hamartoma [21, 22]. Nearly 85% are solitary and about 10% of patients have more than two nodules [23]. Allair et al. [1] recorded 152 cases from the files of the United States Armed Forces Institute of Pathology for the years 1943 to 1986, which is the largest series of BDAs to date.

Histologically, BDA consists of slightly dilated ductules with various amounts of lymphocyte infiltration and fibrosis. The clinical significance of BDA lies in its potential for confusion with malignant neoplasms or other benign lesions. BDA and BDH have an overlapping histological pattern, and a differential diagnosis between them may be difficult [19]. Histologically observed ductules with cystic dilatation or showing brown bile plugs are more typical of BDH than BDA [1]. BDH (also known as von Meyenburg complexes) is often multiple, varying in diameter from 0.1 to 0.5 cm. The malig-

nant transformation of BDH has been described, leading to the hypothesis that BDH may be premalignant. Recently, Pujals et al. [20] confirmed that more than 50% of BDAs were detected with *BRAF* V600E mutations. However, the same mutations occur in a few cases of ICC (no more than 5%) [19].

Two of our cases newly reported here had V600E mutations of *BRAF*. This suggests that BDAs are true neoplastic lesions other than reactive proliferation, and they may be precursors for ICCs. *BRAF* encodes b-raf, a member of the raf/mil family (serine/threonine protein kinases). These proteins regulate the MAPK (mitogen-activated protein kinase)/EPK (extracellular-signal-regulated kinase) signaling pathway, which figures importantly in cell growth, differentiation, and survival [24]. The mutations induce high levels of phosphorylated ERK1/2, a marker of MAPK/ERK signaling pathway activation [24]. The mutations of *BRAF* detected in BDA may also suggest that *BRAF* mutations are an early event in cholangiocarcinogenesis, as seen in colon cancer [19].

The pathogenesis of BDA remains obscure. Since one distinct feature of BDA is pyloric gland metaplasia, it has been suggested that BDA may develop as a focal biliary reactive proliferation, similar to the role of the pyloric gland or peribiliary gland metaplasia in the foregut [22]. Atypical ductular proliferation of peribiliary glands around the major ducts are commonly observed when there are inflammatory injuries [25]. Several recent investigations have found that some cholangiocarcinomas may display features of a Brunner or pyloric gland cell phenotype, as observed in metaplastic peribiliary glands [26]. Based on these observations, Cardinale et al. [27, 28] proposed that the peribiliary gland that displays a mucinous metaplasia may be pre-cancerous, and some mucin-producing cholangiocarcinoma may be derived from progenitor/stem cells of the biliary tree that are located in peribiliary glands. BDA and peribiliary glands test positive for MUC6 [29]. Our cases also showed MUC6 positivity. This suggests that some cholangiocarcinomas may originate from the peribiliary gland.

In the 4 cases newly presented here, lesional areas showing characteristics of either BDA or cholangiocarcinoma were identified. More importantly, transitional zones between the BDA and cholangiocarcinoma were seen histologically. Immunostaining further revealed that atypical ductules in cholangiocarcinoma expressed high levels of HER2, which is regarded as a marker for cholangiocarcinogenesis [30]. In contrast to the CD56 positivity of BDAs, most atypical ductules in cholangiocarcinoma were negative for this marker [31]. This suggests the malignant (or premalignant) nature of BDA cells. CD56 positivity has been demonstrated in BDA [32]. Therefore, in the present 4 cases the combined findings gained from both morphological observation and immunostaining led to diagnoses of cholangiocarcinoma arising from BDA.

So far, only several studies have reported cholangiocarcinoma derived from BDA [7-11], including one case of ICC arising in BDA with a focal area of BDH [9]. The lack of reports regarding malignant transformation of BDA may be because lesions were detected early while still small, or malignant potential was not considered. Recently, cholangiocarcinomas with BDH were described as ICC with a DPM pattern, a new subtype of ICC [33]. One of our present cases show the same pattern in some areas. Kwon et al. [11] observed the same phenomenon in their case. Nakanuma et al. [34] confirmed that there were foci of BDA-like lesions in some peripheral ICCs. BDAs exhibit neoplastic potential with subsequent classical peripheral ICC. When diagnosis is performed by intraoperative frozen section in which only a small portion of the tumor tissue is sampled, clarification of the presence of cholangiocarcinoma arising in BDA may help prevent underdiagnosis.

Typically, ICC has the worst prognosis of carcinomas arising in the liver; the overall 5-year survival rate is 13%-42% [35], and the recurrence rate is high. The median survival after conservative therapy was only 1.8 months, and 12.2 months after surgical resection [16]. In contrast, patients with cholangiocarcinoma from BDA reported by us and other groups showed better survival. However, whether BDA-derived cholangiocarcinoma is a distinct entity with good prognosis requires long-term follow-up in a larger sample.

In conclusion, cholangiocarcinoma can develop from BDA, indicating that BDA may be a precancerous lesion with the potential for malignant

transformation. The classic adenoma-carcinoma sequence linked to *BRAF* mutations in other cancers may occur in cholangiocarcinogenesis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ying Yuan, Department of Pathology, Chinese PLA General Hospital, Beijing 100853, China. Tel: +86-10-66936652-808; E-mail: yuanjing301@126.com

References

[1] Allaire GS, Rabin L, Ishak KG, Sesterhenn IA. Bile duct adenoma. A study of 152 cases. Am J Surg Pathol 1988; 12: 708-715.

[2] Cho C, Rullis I, Rogers LS. Bile duct adenomas as liver nodules. Arch Surg 1978; 113: 272-274.

[3] Karhunen PJ. Benign hepatic tumors and tumor-like conditions in men. J Clin Pathol 1986; 39: 193-198.

[4] Eguchi S, Tajima Y, Yanaga K, Okudaira S, Furui J, Hayashi T, Kanematsu T. Hilar bile duct cancer associated with preoperatively undetectable von Meyenburg complex-report of a case. Hepatogastroenterology 2004; 51: 1301-1303.

[5] Neto AG, Dainiak C, Qin L, Salem RR, Jain D. Intraductal papillary cholangiocarcinoma associated with von Meyenberg complexes: a case report. Dig Dis Sci 2007; 52: 2643-2645

[6] 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: 580-584.

[7] Börnfors M. The development of cholangiocarcinoma from multiple bile-duct adenomas. Report of a case and review of the literature. Acta Pathol Microbiol Immunol Scand A 1984; 92: 285-9.

[8] Foucar E. Bile duct adenoma. Arch Pathol Lab Med 1985; 109: 590-591.

[9] Hasebe T, Sakamoto M, Mukai K, Kawano N, Konishi M, Ryu M, Fukamachi S, Hirohashi S. Cholangiocarcinoma arising in bile duct adenoma with focal area of bile duct hamartoma. Virchows Archiv 1995; 426: 209-213.

[10] Pinho AC, Melo RB, Oliveira M, Almeida M, Lopes J, Graça L, Costa-Maia J. Adenoma-carcinoma sequence in intrahepatic cholangiocarcinoma. Int J Surg Case Rep 2012; 3: 131-3.

[11] Kwon AY, Lee HJ, An HJ Kang H, Heo JH, Kim G. Intrahepatic Cholangiocarcinoma with Ductal Plate Malformation-like Feature Associated with Bile Duct Adenoma. J Pathol Transl Med 2015; 49: 531-534.

[12] Nakanuma Y, Curado MP, Franceschi S, Gores G, Paradis V, Sripa B, Tsui WMS, Wee A. intrahepatic cholangiocarcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. World Health Organization classification of tumours: pathology and genetics of tumours of the digestive system. Lyon: IARC Press; 2010. pp. 217-225.

[13] Kämmerer U, Kapp M, Gassel AM, Richter T, Tank C, Dietl J, Ruck P. A new rapid immunohistochemical staining technique using the EnVision antibody complex. J Histochem Cytochem 2001; 49: 623-30

[14] Choi HJ, Kim HJ, Choi JH. Expression of c-erbB-2 and Cyclooxygenase-2 in intrahepatic cholangiocarcinoma. Hepato-Gastroenterology 2009; 56: 606-609.

[15] Lu J, Gao J, Zhang J, Sun J, Wu H, Shi X, Teng L, Liang Z. Association between BRAF V600E mutation and regional lymph node metastasis in papillary thyroid carcinoma. Int J Clin Exp Pathol 2015; 8: 793-9.

[16] Chu KM, Lai EC, Al-Hadeedi S, Arcilla CE Jr, Lo CM, Liu CL, Fan ST, Wong J. Intrahepatic cholangiocarcinoma. World J Surg 1997; 21: 301-305; discussion 305-306.

[17] Stacey E Mills, Darryl Carter, Joel K Greenson, Harold A Oberman, Victor Reuter, Mark H Stoler. STERNBERG'S Diagnostic Surgical Pathology (Fourth Edition). LIPPINCOTT WILLIAMS & WILKINS 530 Walnut street Philadelphia, PA 19106 USA 2004. pp. 1747-1749.

[18] Aishima S, Tanaka Y, Kubo Y, Shirabe K, Maehara Y, Oda Y. Bile duct adenoma and von Meyenburg complex-like duct arising in hepatitis and cirrhosis: pathogenesis and histological characteristics. Pathol Int 2014; 64: 551-9.

[19] Pujals A, Bioulac-Sage P, Castain C, Charpy C, Zafrani ES, Calderaro J. BRAF V600E mutational status in bile duct adenomas and hamartomas. Histopathology 2015; 67: 562-7.

[20] Pujals A, Amaddeo G, Castain C, Bioulac-Sage P, Compagnon P, Zucman-Rossi J, Azoulay D, Leroy K, Zafrani ES, Calderaro J. BRAF V600E Mutations in Bile Duct Adenomas. Hepatology 2015; 61: 403-5.

[21] Bhathal PS, Hughes NR, Goodman ZD. The So-Called Bile Duct Adenoma Is a Peribiliary Gland Hamartoma. Am J Surg Pathol 1996; 20: 858-64.

[22] Hughes NR, Goodman ZD, Bhathal PS. An Immunohistochemical Profile of the So-called Bile Duct Adenoma: Clues to Pathogenesis. Am J Surg Pathol 2010; 34: 1312-1318.

[23] Ishak KG, Goodman ZD, Stocker JT. Tumors of the liver and intrahepatic bile ducts. In: Rosai

J, Sobin LH, editors. Atlas of tumor pathology. 3rd edition. fascicle 31.Washington, DC: Armed Forces Institute of Pathology; 2001.
[24] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature 2002; 417: 949-954.
[25] Goodman ZD. Neoplasms of the liver. Mod Pathol 2007; 20 Suppl 1: S49-60.
[26] Hughes NR, Pairojkul C, Royce SG, Clouston A, Bhathal PS. Liver fluke-associated and sporadic cholangiocarcinoma: an immunohistochemical study of bile duct, peribiliary gland and tumour cell phenotypes. J Clin Pathol 2006; 59: 1073-8.
[27] Cardinale V, Wang Y, Carpino G, Cui CB, Gatto M, Rossi M, Berloco PB, Cantafora A, Wauthier E, Furth ME, Inverardi L, Dominguez-Bendala J, Ricordi C, Gerber D, Gaudio E, Alvaro D, Reid L. Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. Hepatology 2011; 54: 2159-2172.
[28] Cardinale V, Wang Y, Carpino G, Reid LM, Gaudio E, Alvaro D. Mucin-Producing Cholangiocarcinoma Might Derive from Biliary Tree Stem/Progenitor Cells Located in Peribiliary Glands. Hepatology 2012; 55: 2041-2.
[29] Aishima S, Tanaka Y, Kubo Y, Shirabe K, Maehara Y, Oda Y. Bile duct adenoma and von Meyenburg complex-like duct arising in hepatitis and cirrhosis: pathogenesis and histological characteristics. Pathol Int 2014; 64: 551-9.
[30] Sirica AE. Role of ErbB family receptor tyrosine kinases in intrahepatic cholangiocarcinoma. World J Gastroenterol 2008; 14: 7033-58.
[31] Gütgemann I, Haas S, Berg JP, Zhou H, Büttner R, Fischer HP. CD56 expression aids in the differential diagnosis of cholangiocarcinomas and benign cholangiocellular lesions. Virchows Arch 2006; 448: 407-11.
[32] Wei J, Zhang D, Yang J, Xu C. Intrahepatic bile duct adenoma (peribiliary gland hamartoma): a case report and review of literature. Int J Clin Exp Pathol 2015; 8: 5908-13.
[33] Nakanuma Y, Sato Y, Ikeda H, Harada K, Kobayashi M, Sano K, Uehara T, Yamamoto M, Ariizumi S, Park YN, Choi JH, Yu E. Intrahepatic cholangiocarcinoma with predominant "ductal plate malformation" pattern: a new subtype. Am J Surg Pathol 2012; 36: 1629-35.
[34] Nakanuma Y, Tsutsui A, Ren XS, Harada K, Sato Y, Sasaki M. What are the precursor and early lesions of peripheral intrahepatic cholangiocarcinoma? Int J Hepatol 2014; 2014: 805973.
[35] Yang J, Yan LN. Current status of intrahepatic cholangiocarcinoma. World J Gastroenterol 2008; 14: 6289-97.