

# Biliary intraepithelial neoplasia: a case with benign biliary stricture

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## INTRODUCTION

Intrahepatic and extrahepatic cholangiocarcinomas develop through a multistep carcinogenesis sequence and they are preceded by precursor lesions. Precursors of malignant neoplasm are identified in various organs including uterine cervix, gastrointestinal tract and breast. Identification of these precursor lesions are important in that they need minimal treatment or they are good indicator of disease progression or recurrence.

In the intrahepatic and extrahepatic biliary tract, precursor lesions of malignancy are defined as follows; biliary intraepithelial neoplasia (BillIN), intraductal papillary neoplasm, mucinous cystic neoplasm, and adenoma.<sup>1</sup> BillIN is characterized by atypical epithelial cells with multi-layering of nuclei and micropapillary projections into the lumen of bile duct.<sup>2,3</sup> In contrast to intraductal papillary neoplasm which is characterized by papillary proliferation of epithelial cells with fibrovascular stroma and mucin production, BillIN tend to be a microscopic lesion. Mucinous cystic neoplasm is usually cystic lesions and has distinguishing clinicopathologic findings such as subepithelial stroma resembling ovarian stroma and predominant occurrence in adult female. Adenomas are commonly encountered in extrahepatic bile ducts and divided into tubular, papillary and tubulopapillary on the basis of growth pattern.<sup>1</sup>

## CASE SUMMARY

A 70-year-old previously healthy female presented with general weakness. She is a carrier of hepatitis B virus, but has no recent history of hepatitis. The results of a physical examination were unremarkable. Initial serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels were 52 IU/L, 24 IU/L and 47 IU/L, respectively. Serologic marker for hepatitis B surface antigen was positive. Serum alpha-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9 levels were 2.3 ng/mL, 1.2 ng/mL and 7.1 U/mL, respectively. Abdominal ultrasonography and computed tomography revealed dilatation of left intrahepatic bile ducts with focal narrowing of left hepatic duct. Because the possibility of cholangiocarcinoma could not be excluded, the patient submitted to a left lobectomy of liver.

## PATHOLOGIC FINDINGS

On gross examination, liver surface was unremarkable. When bisected along hepatic duct, intrahepatic duct showed cystic dilatation (Fig. 1). Extrahepatic bile duct demonstrated focal narrowing of lumen, but no mass lesion was observed. Microscopically, there was wall thickening with fibrous change at extrahepatic bile duct portion. Cystically dilated intrahepatic bile duct was covered by biliary epithelia

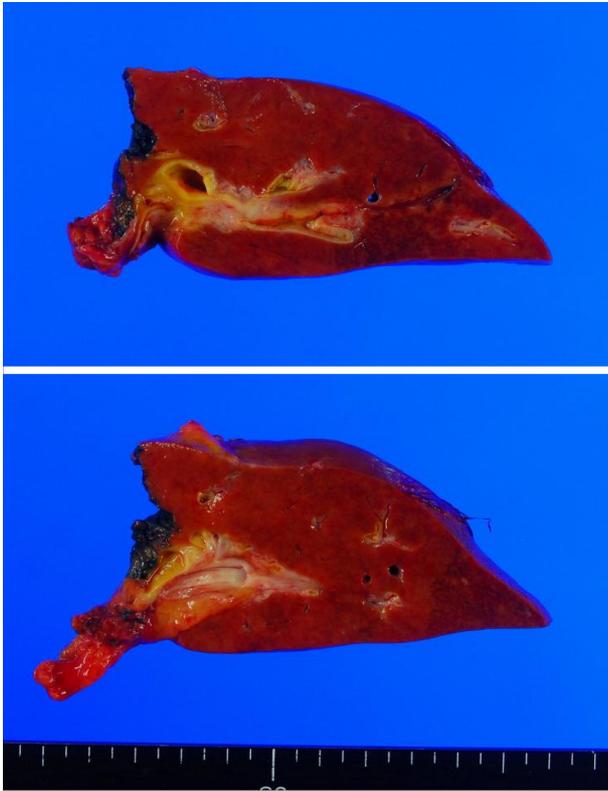
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**Abbreviations:** BillIN, biliary intraepithelial neoplasia

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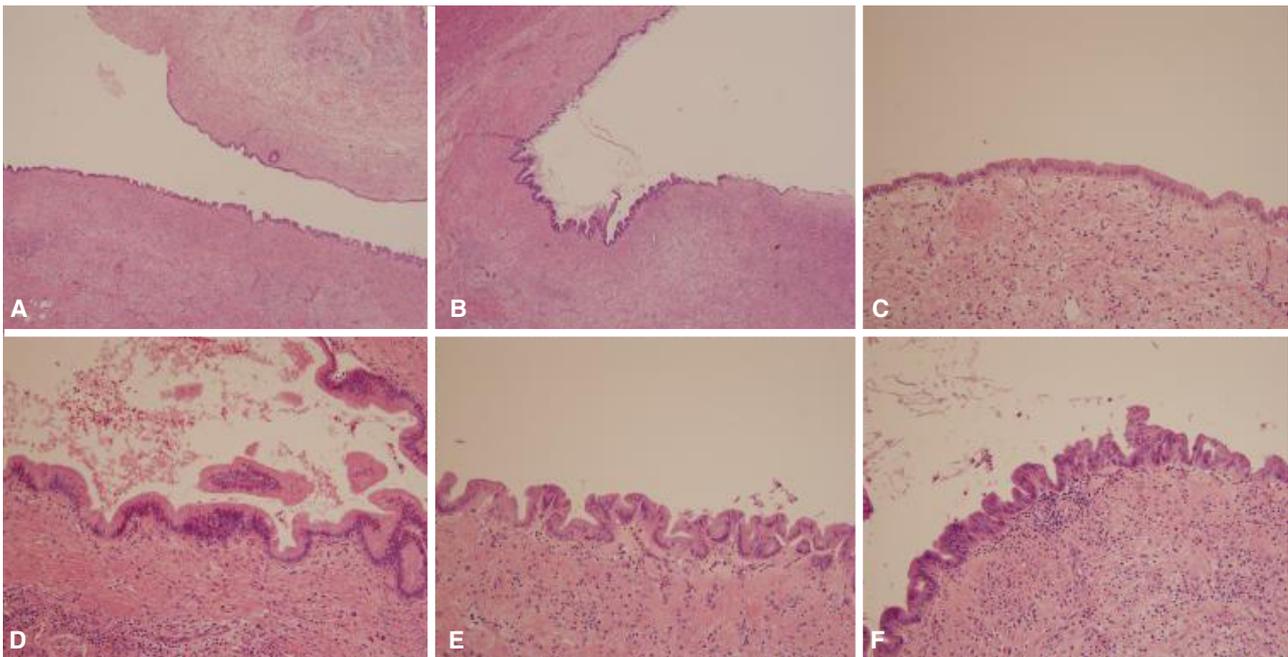


**Figure 1.** Macroscopic picture of the left lobe of the liver. Dilatation of intrahepatic bile ducts is seen without mass lesion.

showing variable degree of atypia (Fig. 2). Epithelial cells lining these lesions were mostly flat, but in some foci, they showed micropapillary or tufted appearance. Pseudostratification of nuclei was commonly finding. Variations in nuclear size, nuclear membrane irregularity and abnormally large nuclei are also noted. Invasion of basal lamina was not observed. This patient was finally diagnosed as biliary intraepithelial neoplasia.

## DISCUSSION

BilIN is not infrequently encountered in routine pathologic practice. In surgically removed liver samples of chronic biliary disease and chronic liver disease such as hepatolithiasis, primary sclerosing cholangitis, choledochal cyst, chronic hepatitis C, and alcoholic cirrhosis, BilINs can be found without difficulty and in which condition, the incidence of cholangiocarcinoma is high.<sup>3-5</sup> BilINs are also frequently found in adjacent to invasive cholangiocarcinomas and the incidence of BilIN-3 lesion parallels that of invasive cholangiocarcinoma suggesting that BilIN could be precursor lesion of invasive cholangiocarcinoma.<sup>1</sup> There is a report



**Figure 2.** Histologic features of bile duct epithelium lining dilated bile ducts. (A, B) Normal epithelium and biliary intraepithelial neoplasia (BilINs) are observed. (C) Normal biliary epithelia show monolayer of columnar cells without pseudostratification. (D) Focal nuclear pseudostratification and nuclear elongation are noted. Nuclear sizes and shapes are relatively uniform (BilIN-1). (E) This lesion shows tufted epithelial structure. Nuclear enlargement and irregular nuclear membrane are evident (BilIN-2). (F) Cytologic and nuclear abnormality including loss of polarity, nuclear enlargement and nuclear membrane irregularity are evident. There is no invasion of basement membrane (BilIN-3). (A and B: hematoxylin and eosin (H&E),  $\times 40$ ; C-F: H&E,  $\times 400$ ).

about progression of BilIN to invasive cholangiocarcinoma in which immunohistochemical staining of p21, p53 and cyclin-D1 antibodies revealed up-regulation of these proteins with histological progression from BilIN to invasive cholangiocarcinoma.<sup>6</sup> A molecular study also revealed stepwise increase of promoter CpG island methylation and decrease of repetitive element methylation in BilIN-cholangiocarcinoma sequence.<sup>7</sup>

BilIN is usually not recognized on macroscopic examination. On macroscopic examination, mucosa shows only discolored, granular or plaque-like appearance. Microscopically, BilIN shows enlargement of cells, pseudostratification and micropapillae formation.<sup>1-3</sup> According to the degree of cytological and architectural atypia, BilINs are divided into BilIN-1, BilIN-2 and BilIN-3. BilIN-1 correspond to low grade lesion (ICD-O code, 8148/0), BilIN-2 to intermediate lesion (ICD-O code, 8148/0) and BilIN-3 to high grade lesion (ICD-O code, 8148/2).<sup>1</sup> Some of hyperplastic or regenerative change could show cytological and structural features resembling BilINs, but these lesions lack sufficient atypia to be regarded as neoplastic.

Precursor lesions of intra- and extrahepatic biliary tract are not easily accessible due to the anatomic location, so it is difficult to get biopsy samples through endoscopic or needle biopsy. Furthermore, BilIN is mostly flat or micropapillary lesion that neither form mass lesion nor cause bile duct obstruction. Early detection or regular follow up of BilIN is very difficult. This is why the natural course or prognosis of BilIN is not well understood. Till now, the knowledge and clinical utilization of BilIN is limited. But it can provide the information about carcinogenesis of cholangiocarcinoma and this classification of precursor lesion of malignancy could be applicable to clinical or pathologic studies of biliary

epithelium and to evaluation of patients with hepatolithiasis, choledocal cyst and primary sclerosing cholangitis patients. So, it is hoped that understanding of BilIN could be able to help us better understand of biliary tract neoplasia.

This case shows variable degree of BilINs at cystically dilated intrahepatic bile duct proximal to benign stricture of extrahepatic bile duct. These findings suggest that chronic stimuli at bile duct epithelium could promote dysplastic change and these stimuli may be the cause of development of cholangiocarcinoma.

## REFERENCES

1. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer, 2010:222-223,270-271.
2. Zen Y, Aishima S, Ajioka Y, Haratake J, Kage M, Kondo F, et al. Proposal of histological criteria for intraepithelial atypical/proliferative biliary epithelial lesions of the bile duct in hepatolithiasis with respect to cholangiocarcinoma: preliminary report based on interobserver agreement. *Pathol Int* 2005;55:180-188.
3. Zen Y, Adsay NV, Bardadin K, Colombari R, Ferrell L, Haga H, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. *Mod Pathol* 2007;20:701-709.
4. Wu TT, Levy M, Correa AM, Rosen CB, Abraham SC. Biliary intraepithelial neoplasia in patients without chronic biliary disease: analysis of liver explants with alcoholic cirrhosis, hepatitis C infection, and noncirrhotic liver diseases. *Cancer* 2009;115:4564-4575.
5. Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC. Precancerous bile duct pathology in end-stage primary sclerosing cholangitis, with and without cholangiocarcinoma. *Am J Surg Pathol* 2010;34:27-34.
6. Nakanuma Y, Sasaki M, Sato Y, Ren X, Ikeda H, Harada K. Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. *World J Hepatol* 2009;1:35-42.
7. Kim BH, Cho NY, Shin SH, Kwon HJ, Jang JJ, Kang GH. CpG island hypermethylation and repetitive DNA hypomethylation in premalignant lesion of extrahepatic cholangiocarcinoma. *Virchows Arch* 2009;455:343-351.