

## CASE REPORT

# Hilar cholangiocarcinoma accompanied by pancreaticobiliary maljunction without bile duct dilatation 20 years after cholecystectomy : report of a case

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**Abstract :** Pancreaticobiliary maljunction (PBM) is associated with the occurrence of biliary cancer due to pancreatobiliary reflux. From the perspective of carcinogenesis, the treatment for PBM is controversial. We herein report a case of hilar cholangiocarcinoma 20 years after the occurrence of gallbladder cancer. A 75-year-old man was referred to our hospital regarding an obstructive jaundice and bile duct tumor. A cholecystectomy was performed for cholelithiasis on this patient 20 years ago, and cancer in situ was detected. Computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) revealed a tumor of the portal hepatic region and PBM without dilatation of the bile duct. Adenocarcinoma was detected from bile cytology, and we diagnosed hilar cholangiocarcinoma. Despite the biliary decompression, jaundice was prolonged and the patient passed away. Our case suggests that not only cholecystectomy but also biliary diversion is needed for PBM regardless of the existence of bile duct dilatation. *J. Med. Invest.* 60 : 169-173, February, 2013

**Keywords :** *pancreaticobiliary maljunction, hilar cholangiocarcinoma, cholecystectomy*

## INTRODUCTION

Pancreaticobiliary maljunction (PBM) is a congenital anomaly defined as a union of the pancreatic and biliary ducts outside of the duodenal wall (1-3). The most important clinical feature is the frequent association of PBM with biliary cancers. As the abnormal sphincter muscle cannot functionally affect the union, two-way regurgitation (pancreatobiliary and biliopancreatic reflux) occurs, resulting in various pathological conditions in the

biliary tract and pancreas (1-3). As the hydropressure in the pancreatic duct is usually higher than in the bile duct (4), pancreatic juice frequently refluxes into the bile duct through the anomalous junction, resulting in a high incidence of carcinogenesis in the biliary tract. From the perspective of carcinogenesis, the treatment of PBM especially without bile duct dilatation is controversial ; either only a cholecystectomy should be performed, in which case an extrahepatic biliary duct resection would be unnecessary, or both an extrahepatic biliary duct resection and hepaticojejunostomy should be undertaken. We herein report a case of hilar cholangiocarcinoma that occurred 20 years after cholecystectomy for incidental gallbladder cancer, with PBM.

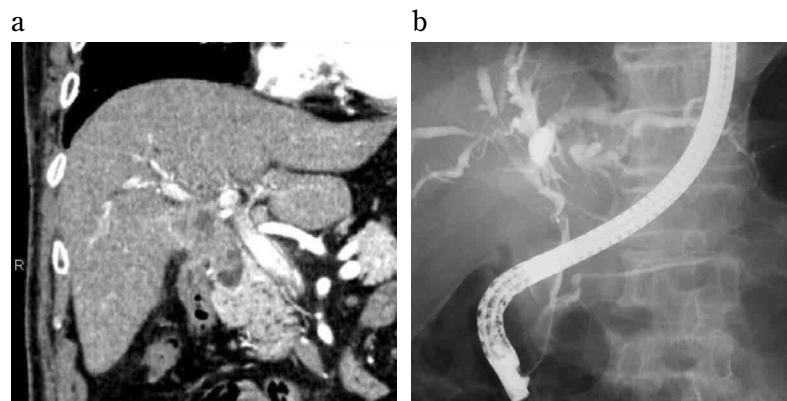
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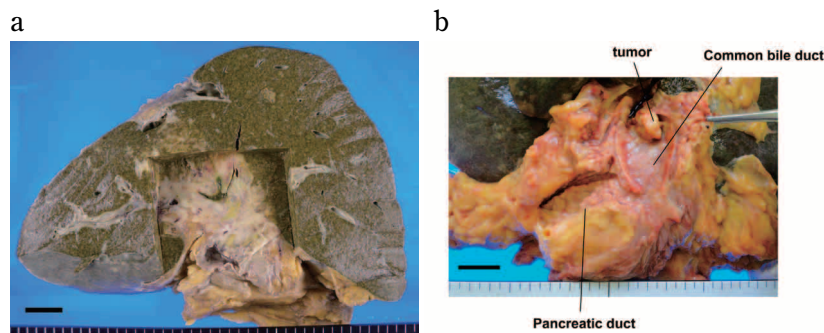
## CASE REPORT

A 75-year-old male was referred to our institute for jaundice and a tumor of the common bile duct. He was performed a cholecystectomy for cholelithiasis 20 years ago at a nearby hospital, and the histological finding revealed that the gallbladder had well-differentiated adenocarcinoma in situ. As further examinations of the biliary tract were not undertaken, the existence of pancreaticobiliary maljunction (PBM) was not found at that time. In December 2010, the patient went to the hospital for general malaise and was diagnosed with jaundice. MRCP revealed a tumor in the hepatic portal region and dilatation of the intrahepatic bile duct. He was admitted to our institute, and examinations of the tumor were performed. Abdominal computed tomography (CT) showed a space occupied with lesions from the hilar to middle bile duct, with enhancement and intrahepatic bile duct dilatation (Figure 1a). Endoscopic retrograde cholangiopancreatography (ERCP) revealed stenosis of the hilar~middle bile duct because of the tumor (Figure 1b).

ERCP also showed that the main pancreatic duct joined the bile duct above the papilla of Vater (classification of PBM type B, Figure 1b). The diameter of the common bile duct was 10 mm. In light of the dilatation caused by the bile duct obstruction resulting from the tumor, we diagnosed PBM without dilatation of the bile duct. We performed endoscopic retrograde biliary drainage and adenocarcinoma was detected from bile cytology. We diagnosed hilar cholangiocarcinoma with PBM. As the abdominal CT showed swelling of the paraaortic lymph nodes, we decided that the operation could not be performed. For biliary decompression, an endoscopic retrograde biliary drainage (ERBD) tube was placed in the right hepatic duct. However, biliary decompression was not achieved with complete success due to the tumor in the hepatic portal region. The patient's general condition gradually worsened, and he passed away three months after admission. The diagnosis from the autopsy was hilar cholangiocarcinoma and pancreaticobiliary maljunction (Figure 2 a, b). In the specimen obtained from the autopsy, HE staining showed that the tumor in the hepatic



**Figure 1.** Findings of liver and bile duct. (a) findings of contrast enhanced CT. There is a tumor from the hepatic portal region to the middle bile duct with enhancement and intrahepatic bile duct dilatation. (b) findings of ERCP. Tumor causes stenosis of the hepatic portal region ~ middle bile duct, and the main pancreatic duct joined the bile duct above the papilla of Vater (classification of PBM type B).



**Figure 2.** Specimen of autopsy. (a) total image of the liver. (b) findings of tumor invasion to middle bile duct and pancreaticobiliary maljunction. Scale bars, 2 cm. Diagnosis was hilar cholangiocarcinoma and pancreaticobiliary maljunction.

portal region extended to the middle of the common bile duct (Figure 3a, b). K-ras and HDAC antibody staining were positive both in the cancerous part and non-cancerous part (Figure 4a-d).

### DISCUSSION

The pathological condition of PBM is such that the mixing of phospholipase A2 in pancreatic juice

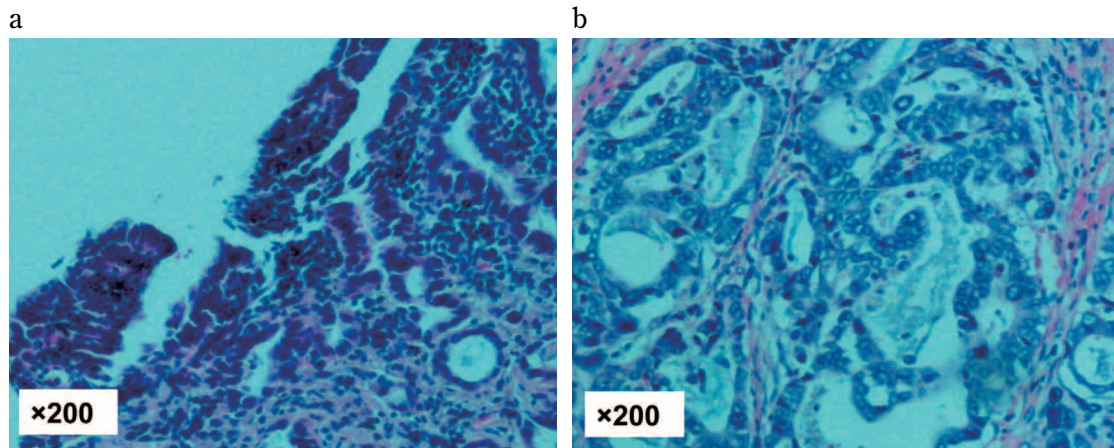


Figure 3. HE staining of cancerous part. (a) common bile duct, ×200 (b) hepatic portal region, ×200

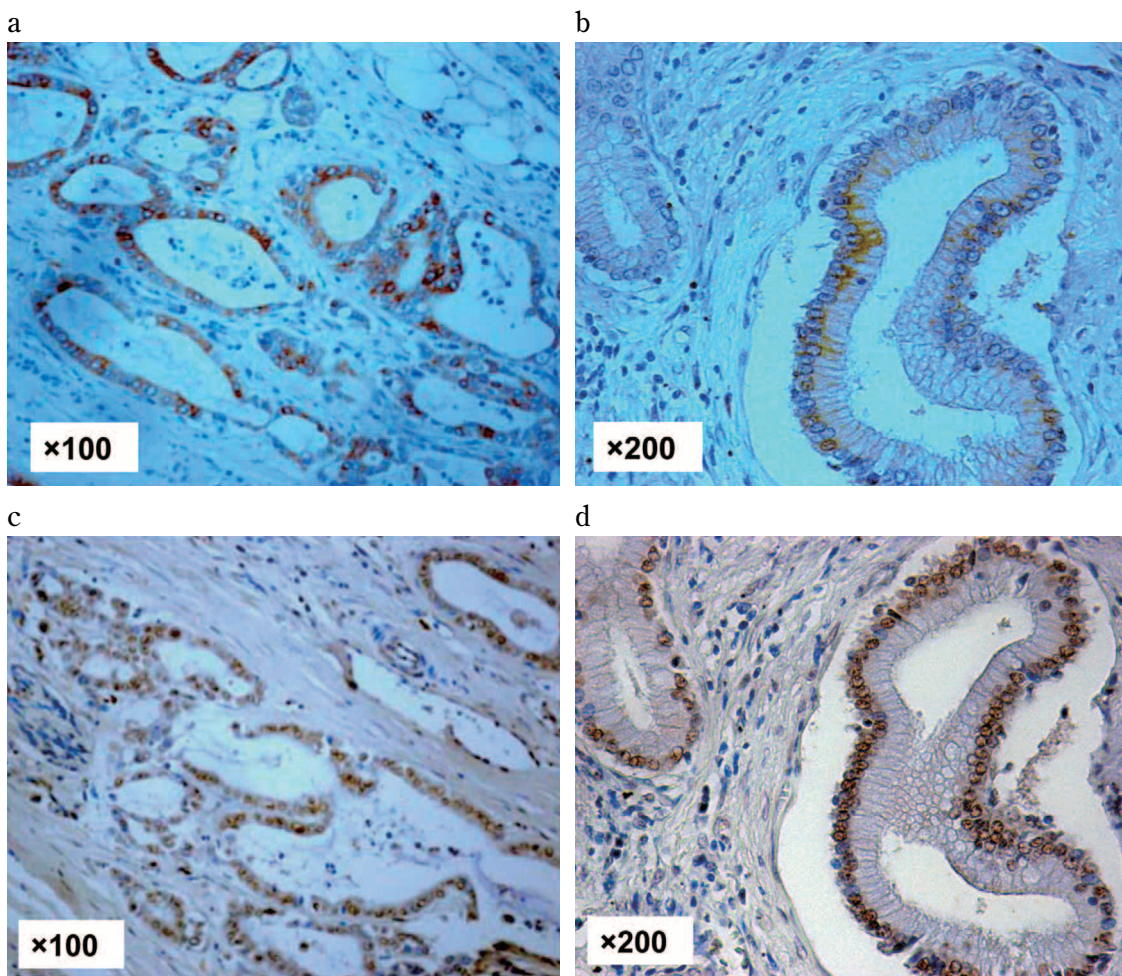


Figure 4. Immunohistochemical findings for k-ras and HDAC (a,b : k-ras, c,d : HDAC). (a) cancerous part, ×100 (b) non cancerous part, ×200 (intrahepatic bile duct) (c) cancerous part, ×100 (d) non cancerous part, ×200 (intrahepatic bile duct)

and bile will produces lysolecithin, which has severe cell toxicity. Repeated damage to, and restoration of, the biliary epithelium produces a variant accompanied by cellular atypical change (5), displaying a hyperplasia-dysplasia-carcinoma sequence (6, 7). From the perspective of carcinogenesis, the treatment of PBM, especially without bile duct dilatation, is controversial; either only a cholecystectomy should be performed, in which case an extrahepatic biliary duct resection would be unnecessary, or both an extrahepatic biliary duct resection and hepaticojejunostomy should be performed. It was reported that the cancer development rates of PBM in adults with dilatation of bile duct are 13.4% in the gallbladder, 7.0% in the bile duct, and 1.0% in the gallbladder+bile duct (8). Those of PBM without dilatation of the bile duct are 37.4% in the gallbladder, 3.1% in the bile duct, and 1.8% in the gallbladder+bile duct (8). This report has revealed that PBM has a background of biliary tract carcinogenesis regardless of whether it is with or without bile duct dilatation, and that we should pay attention to the carcinogenesis of the gallbladder in particular. Although the carcinogenesis rate of an undilated bile duct with PBM was the lowest among these data (3.1%), this rate is 200 times higher than that seen in usual carcinogenesis of the bile duct in Japan (9). These facts suggest that biliary diversion is necessary in the light of carcinogenesis. In terms of complication of biliary diversion, acute pancreatitis, pancreatic fistula, gastrointestinal bleeding and ileus can occur as early complication. However, these complications occur with low frequency and most of them recover by conservative management. Cholangitis and hepatolithiasis are reported to occur as late complication, and induced mainly by bile duct stenosis (10). As these complications can occur repeatedly, careful, long-term follow-up is important. About the molecular mechanism of carcinogenesis, K-ras are mainly discussed as a gene abnormality of mucosal epithelium. The genetic mutation of K-ras in the cancerous parts of early gallbladder cancer with PBM is seen at a level of 50%, higher than that of usual early gallbladder cancer (6%) (11). In terms of bile duct cancer, it was reported that K-ras mutation with PBM was detected at 60-100% in cancerous parts and at 40% in the non-cancerous parts with or without dilatation of the bile duct (12, 13). In our case, since K-ras antibody staining was positive both in the cancerous and non-cancerous parts, there could have been a high potential for carcinogenesis in the bile duct.

From an epigenetic perspective, the status of histone acetylation, which is controlled by histone acetyltransferase (HAT) and histone deacetylase (HDAC), plays an important role in various gene expressions through the chromatin remodeling. Specifically, the aberrant activation of HDAC in tumor cells leads to diverse transcriptional gene repression, mainly involving the regulation of differentiation, angiogenesis, proliferation, migration, and metastasis (14, 15). Furthermore, it was reported that HDAC inhibitor decrease the expression of k-ras (16), and HDAC may influence on k-ras activity in mechanism of carcinogenesis. In our case, HDAC staining was positive both in the cancerous and non cancerous parts. Repeated damage to, and restoration of, the biliary epithelium, can lead to aberrant activation of HDAC, and relate to the overexpression of k-ras and potential for carcinogenesis.

In conclusion, we experienced a case of hilar cholangiocarcinoma with PBM 20 years after the occurrence of gallbladder cancer, and we suggest that surgery to separate the pancreatic juice and bile along with a cholecystectomy is needed for PBM, regardless of the existence or otherwise of bile duct dilatation.

## CONFLICT OF INTEREST STATEMENT

Shinichiro Yamada and other co-authors have no conflict of interest.

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