

Precancerous Pyloric Gland Metaplasia in the Biliary Epithelium Associated with Congenital Biliary Dilatation in a Three-Month-Old Infant

Shuichi Takano,* Toshimichi Hasegawa,* Kohga Masuda,* Takehiko Hanaki,* Naruo Tokuyasu,* Teruhisa Sakamoto,* Kanae Nosaka† and Yoshiyuki Fujiwara*

*Department of Gastrointestinal and Pediatric Surgery, School of Medicine, Faculty of Medicine, Tottori University, Yonago 683-8504, Japan and †Department of Pathology, School of Medicine, Faculty of Medicine, Tottori University, Yonago 683-8504, Japan

ABSTRACT

Pyloric gland metaplasia in the biliary epithelium is a precancerous lesion and has been confirmed in patients with congenital biliary dilatation presenting with overt biliary tract cancer. A patient was found to have an intra-abdominal cyst on fetal ultrasonography and was born at 37 weeks of gestation with a body weight of 2,636 g. Abdominal distension and repeated vomiting appeared 2 days after birth. Congenital biliary dilatation was diagnosed by imaging, wherein the common bile duct was enlarged to 9–10 cm in size, and the surrounding organs were extensively compressed; however, there was no sign of pancreatitis or cholangitis. Biliary drainage was performed through the gallbladder at 6 days of age, but it was insufficient because of the narrow and twisted cystic duct and changed to common bile duct at 18 days to relieve the compression. Because the body weight gain was poor due to loss of large amount of bile, the dilated bile duct and gallbladder were resected and hepatic duct Roux-Y jejunostomy was performed at 115 days of age with 4,500 g of body weight. Intraoperative imaging showed a pancreaticobiliary maljunction, and the pancreatic enzyme activities of the bile in the biliary system were remarkably elevated. Histopathological examination revealed pyloric gland metaplasia in the gallbladder epithelium and cystic duct. The patient is now over 2 years old and has been doing well without any complications. Based on our experience, precancerous pyloric gland metaplasia of the biliary epithelium may already occur even in a 3-month-old infant presenting with congenital biliary dilatation.

Key words biliary tract cancer; congenital biliary dilatation; pancreaticobiliary maljunction; precancerous lesion; pyloric gland metaplasia

Corresponding author: Toshimichi Hasegawa, MD, PhD
t.hasegawa@tottori-u.ac.jp

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Abbreviations: CBD, congenital biliary dilatation; MRCP, Magnetic Resonance Cholangiopancreatography; PBM, pancreaticobiliary maljunction; PLA₂, phospholipase A₂

Congenital biliary dilatation (CBD) is known to be associated with biliary tract cancer and is thought to be caused by an injured substance generated by mixing pancreatic juice and bile due to the accompanying pancreaticobiliary maljunction (PBM).^{1–7} Although the risk of cancer is high in adults, there have been a few reports of children presenting with biliary tract cancer,^{1, 8, 9} and so far, the youngest case with cancer was of a 3-year-old boy.¹⁰ Precancerous lesions have been reported to be a hyperplasia or metaplasia of the epithelium of biliary system, such as intestinal and pyloric gland metaplasia.^{3, 11–16} However, precancerous lesions in young infants have not been investigated as much.^{17, 18} Here, we report a case of pyloric gland metaplasia in the resected biliary epithelium in a 3-month-old infant with CBD.

PATIENT REPORT

Prenatal ultrasonography revealed a 14 mm-sized cyst in the abdominal cavity of the fetus at 24 weeks of gestation. A female baby was born by normal delivery at 37 weeks of gestation and weighed 2,636 g. Ultrasonography after birth revealed that her intra-abdominal cyst was 6 cm in size. Two days after birth, she presented with abdominal distension and repeated vomiting. Subsequently, she was admitted to our hospital. Her blood test results were within normal range. Magnetic Resonance Cholangiopancreatography (MRCP) examination showed that the common bile duct was markedly dilated, with a maximum diameter of 8 cm, and the common hepatic duct was slightly dilated (Fig. 1). Gallbladder drainage was performed at the age of 6 days, but it was insufficient because of the narrow and twisted cystic duct and changed to common bile duct drainage at the age of 18 days to relieve compression of the surrounding tissues. Because a significant amount of drainage bile and poor weight gain were observed, the dilated bile duct and gallbladder were resected, and hepatic duct Roux-en-Y jejunostomy was performed at the age of 115 days. The biochemical data of bile in the gallbladder and common bile duct collected during surgery are shown in Table 1. The total bilirubin and amylase levels of the gallbladder bile

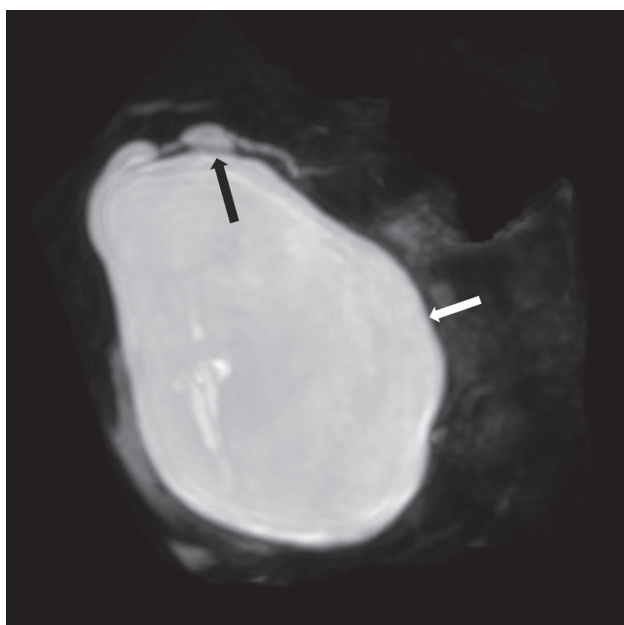


Fig. 1. MRI scan image. The common bile duct is markedly dilated (the white arrow). The black arrow indicates the common hepatic duct.

were within the normal range; however, common bile duct amylase levels were moderately high, and trypsin, phospholipase A₂ (PLA₂), and elastase₁ activities were remarkably elevated, suggesting the presence of PBM. Intraoperative cholangiography showed that the common channel was long and confirmed the presence of PBM (Fig. 2).

Histopathologic investigation revealed scattered erosions in the excised bile duct mucosa with mild to moderate chronic inflammatory cell infiltration (Fig. 3). The mucosal epithelium was preserved in the gallbladder and bile duct, but pyloric gland metaplasia with nuclei deviating from the mucus in the cytoplasm was occasionally observed, presenting evidence of chronic inflammation. No malignant findings were observed. The postoperative course had no complications, and she is now 2 years old with appropriate weight gain.

DISCUSSION

CBD associated with biliary tract cancer is reported to comprise 5–10% of all biliary tract cancers.⁷ The mechanism of malignant transformation is thought to be chronic inflammation due to stasis of pancreatic enzymes in the biliary system activated by the regurgitation of pancreatic juice into the biliary tract from the accompanying PBM.^{2–4, 6, 7} PLA₂ is a highly cytotoxic pancreatic enzyme that hydrolyzes lysophosphatidylcholine (lecithin) to produce more injurious

Table 1. Biochemical data of the bile

| Gallbladder: | | |
|-------------------|-----------|-------|
| T. Bilirubin | 2.2 | mg/dL |
| Amylase | < 1 | IU/L |
| Common bile duct: | | |
| T. Bilirubin | 4.7 | mg/dL |
| Amylase | 1,016 | IU/L |
| Trypsin | 3,670,000 | ng/mL |
| PLA ₂ | 1,420,000 | ng/mL |
| Elastase 1 | 158,000 | ng/mL |

T. Bilirubin, Total bilirubin.

lysophosphatidylcholine (lysolecithin), which may be the main cause of biliary tract cancer.^{19, 20} In the present case, the common bile duct amylase level was moderately high, and trypsin, PLA₂, and elastase₁ activities were markedly high. Moreover, intraoperative cholangiography showed a long common duct and presence of PBM.

The biliary epithelium leads to hyperplasia in the background of chronic inflammation, and dysplasia-carcinoma sequence may form.^{2–4, 11} Furthermore, metaplasia is considered as another carcinogenic lesion, and a metaplasia-dysplasia-carcinoma sequence may form.^{11, 16} In our case, pyloric gland metaplasia was observed in the biliary epithelium and showed evidence that the epithelium had been persistently injured by the activated pancreatic juice.

Gene abnormalities involved in carcinogenesis include increased cell proliferation by the *KRAS* cancer gene and high expression of the *TP53* gene, a tumor suppressor gene.^{12, 21–25} Matsubara et al.¹² found point mutations in the *KRAS* gene in 80% of cancer epithelium, 58% of hyperplasia and metaplasia, and 44% of inflammatory epithelium in the biliary epithelium of PBM cases; however, no mutations were observed in cases without PBM. Based on these investigations, hyperplasia and metaplasia may have genetic abnormalities and may be in a precancerous state. Because metaplasia is a reversible pathology, the altered epithelial lesion in the residual biliary tract may become harmless due to cessation of the regurgitation of pancreatic juice by operation and may not lead to the development of biliary tract cancer.

Although most of cases with CBD are diagnosed in childhood, the onset of biliary tract cancer is extremely rare in children because the accumulation of genetic abnormalities may take time to cause malignancy.²⁶ The incidence of biliary tract cancer development is

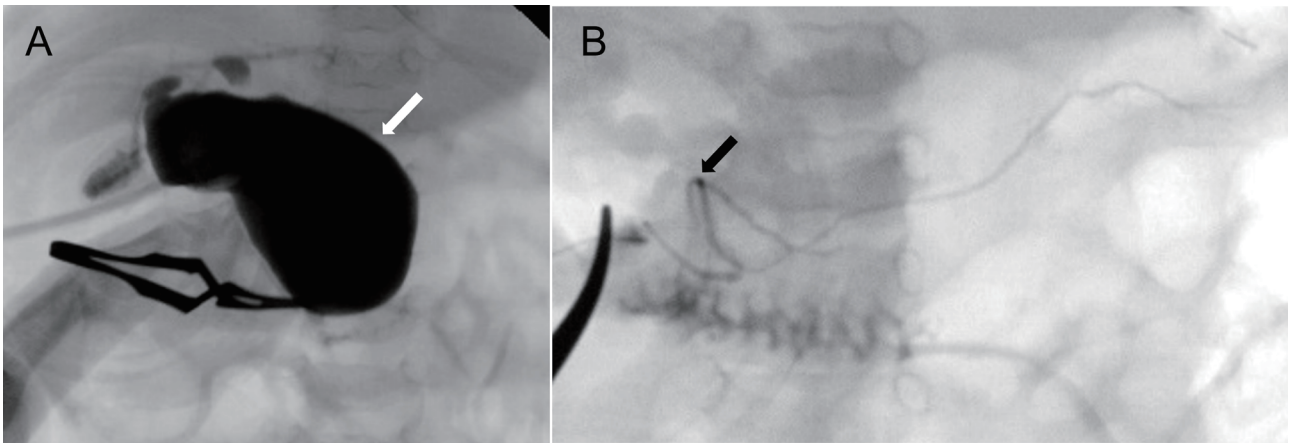


Fig. 2. Intraoperative cholangiography. **A:** The white arrow indicates the extremely dilated common bile duct. **B:** The black arrow indicates the junction of the common bile duct and pancreatic duct.

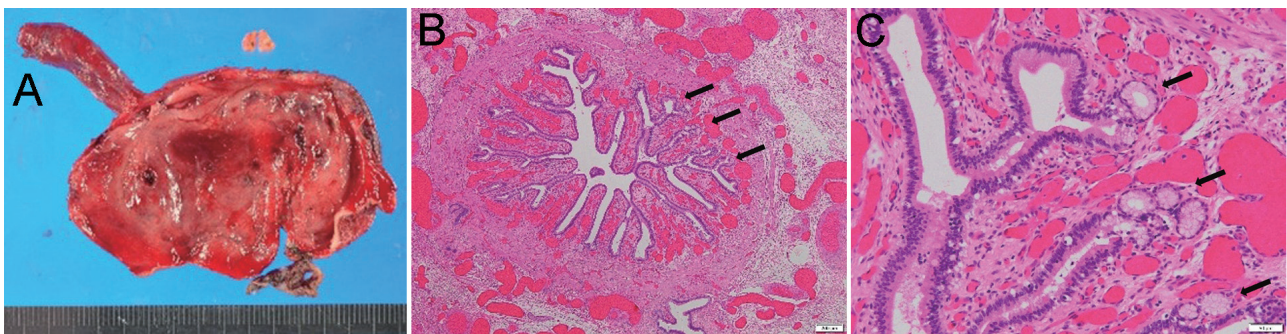


Fig. 3. Pathologic findings of the resected bile ducts and gallbladder. **A:** Macroscopic findings show the erosion and inflammatory changes in the bile duct mucosa. **B** and **C:** Histopathological findings of the bile ducts. Mild to moderate infiltration of the chronic inflammatory cells is observed. Mucosal epithelium is well preserved and pyloric gland metaplasia (black arrow) with flattened nuclei deviating from the mucus in the cytoplasm is observed. No malignant findings are pointed out. Hematoxylin eosin staining. Bar = 200 μm (**B**), 50 μm (**C**).

reported to be less than 1% in children before the age of 10 years.⁹ However, pediatric cases of CBD developing biliary tract cancer have been recently increasing, and the case with the youngest age was of a 3-year-old boy.^{1, 10}

Regarding the metaplasia in PBM, Yamamoto et al.¹¹ reported 26 patients showing metaplasia in the gallbladder mucosa. Katabi et al.¹⁶ described 14 patients with the age of 11 to 67 years presented with metaplasia. Komi et al.¹⁷ showed an increased frequency of epithelial metaplasia of the common bile duct cyst wall with aging and suggested an association with precancerous changes, but metaplasia had not been seen in patients younger than 2 years of age. Ono et al.¹⁸ reported hyperplasia or metaplasia in 24 of 42 (57.1%) PBM cases aged 1 month to 16 years (mean 2.9 years), however, age distribution specific to metaplasia cases was not described and reported that bile amylase levels were significantly

higher in these cases. According to Masuhara et al.,⁸ hyperplasia of the gallbladder epithelium under 3 years of age had no *KRAS* gene abnormality. In the present case, pyloric gland metaplasia of the biliary epithelium had already developed in the 3rd month of life as a pre-cancerous lesion. At the moment, the present case may be the youngest.

These abnormalities may have been due to the persistent exposure of activated pancreatic enzymes during the fetal period. As is generally recognized, the ventral and dorsal pancreas starts to fuse at 6th gestational week and pancreatic juice secrets from acinar cells at 16th week. The extrahepatic bile duct is canalized at 10th week and the lumen of gallbladder opens after 12th week. Secretion of bile begins at 20th week. Therefore, assuming that regurgitation of the pancreatic juice into the bile duct started to mix with bile containing lysophosphatidylcholine (lecithin) since the fetal period,

the present patient may have been exposed to injurious pancreatic juice for at most 9 months. Although the interval of the normal mucosa of the bile duct to form metaplasia has not been discussed in the literature yet, another metaplasia study concerning development of Barrett's esophagus by exposure to gastric acid was made.²⁷ According to Lieberman et al.,²⁷ elective endoscopic examination was regularly performed for 701 patients with gastroesophageal reflux and showed that Odds ratio for the interval to development of Barrett's esophagus was 3.0 in the group presenting symptoms of reflux for 1 to 5 years and 6.4 in the group persisting more than 10 years, compared to the group presenting symptoms for less than 1 year. Accordingly, the interval to development of metaplasia may take more than 1 to 5 years also in CBD with PBM, at least 9 months as in the present case. However, further investigation is needed to elucidate the detailed mechanism of metaplastic changes in the biliary system.

The authors declare no conflict of interest.

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