

Single Case

Peribiliary Gland Hyperplasia That Required Differentiation from Extrahepatic Bile Duct Cancer: A Case Report

Kazuhiro Takami^a Kuniharu Yamamoto^a Hiroto Sakurai^a Yoshihiro Sato^b
Noriko Kondo^a Toru Nakano^b Shingo Tsujinaka^b Akinobu Koiwai^c
Morihiisa Hirota^c Keigo Murakami^d Kazuhiro Murakami^d
Chikashi Shibata^b Yu Katayose^a

^aDivision of Hepato-Biliary-Pancreatic Surgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan; ^bDivision of Gastroenterologic Surgery, Tohoku Medical and Pharmaceutical University, Sendai, Japan; ^cDivision of Gastroenterology, Tohoku Medical and Pharmaceutical University, Sendai, Japan; ^dDivision of Pathology, Tohoku Medical and Pharmaceutical University, Sendai, Japan

Keywords

Peribiliary gland · Hyperplasia · Bile duct cancer

Abstract

Introduction: The peribiliary gland is an accessory bile duct gland. Hyperplasia of these tissues may lead to elevation of the mucosa in the bile ducts and bile duct stenosis. We herein report a case of peribiliary gland hyperplasia that required preoperative differentiation from bile duct cancer, with a discussion of the literature. **Case Presentation:** The patient had an adenomatous lesion in the ascending colon that was difficult to treat endoscopically; therefore, surgery was planned. Preoperative abdominal ultrasonography revealed a bile duct tumor, and endoscopic ultrasonography revealed a mass lesion around the confluence of the cystic duct. Computed tomography revealed localized wall thickening in the middle bile duct, and the upstream bile ducts were slightly dilated. In addition, continuous thickening of the bile duct wall from the gallbladder to the confluence of the cystic duct was observed. No distant metastases, such as liver metastases, or nearby enlarged lymph nodes were observed. Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography revealed a papillary-like elevated lesion in the bile duct near the confluence of the cystic duct, and a biopsy and bile cytology from the same area showed no malignant findings. As a result, the possibility that the patient had gallbladder or bile duct cancer could not be ruled out; therefore, a policy of surgery

Correspondence to:
Kazuhiro Takami, takayan0419@tohoku-mpu.ac.jp

together with the ascending colon tumor was decided after receiving sufficient informed consent. During surgery, the patient underwent extrahepatic bile duct resection, reconstruction of the biliary tract using the Roux-en-Y method, and right hemicolectomy. Both duodenal and hilar bile duct transects were subjected to a fast frozen section analysis during surgery, and the results were negative for cancer. A histopathological examination of the resected specimen revealed no malignant findings in the bile duct lesions, and a diagnosis of peribiliary gland hyperplasia with chronic inflammatory cell infiltration and fibrosis of the extrahepatic bile duct wall was made. **Conclusions:** We encountered a case of peribiliary gland hyperplasia that was difficult to distinguish from bile duct cancer.

© 2024 The Author(s).
Published by S. Karger AG, Basel

Introduction

The peribiliary gland is a bile duct accessory gland included in the wall of the bile duct and has various names, including Beale ducts, Beale glands, deep glands, biliary glands, periductal glands, and extrahepatic peribiliary glands [1–3]. Hyperplasia of these tissues may lead to the elevation of the bile duct mucosa and bile duct stenosis. This is a rare disease, with only 1 case reported to date. We herein report a patient with peribiliary gland hyperplasia that required differentiation from extrahepatic bile duct cancer along with a discussion of the literature.

Case Presentation

The patient was an 80-year-old man with no specific symptoms. Colonoscopy performed by his local doctor revealed two neoplastic lesions in the ascending colon, and he was referred to our hospital for a close examination. Adenoma of the ascending colon was suspected, but because the two lesions were adjacent to each other and accompanied by fibrosis, endoscopic resection was difficult, and surgery was decided.

Abdominal ultrasonography performed preoperatively suggested the presence of a bile duct tumor. Laboratory studies revealed the following findings: leukocyte count, 5,100/ μ L (normal range: 4,000–8,000/ μ L); red blood cell count, 4.30×10^6 / μ L (normal range: $4.4\text{--}5.5 \times 10^6$ / μ L); hemoglobin, 13.1 g/dL (normal range: 14–17 g/dL); total bilirubin, 0.7 mg/dL (normal range: 0.3–1.2 mg/dL); direct bilirubin, 0.1 mg/dL (normal range: 0.1–0.4 mg/dL); aspartate aminotransferase, 20 U/L (normal range: 7–30 U/L); alanine aminotransferase 23 U/L (normal range: 4–30 U/L); alkaline phosphatase, 359 U/L (normal range: 120–370 U/L); total protein, 6.7 g/dL (normal range: 6.7–8.3 g/dL); and total albumin, 3.9 g/dL (normal range: 4.1–5.1 g/dL). The values of the tumor markers CEA and CA19-9 were within normal ranges. Contrast-enhanced computed tomography revealed localized wall thickening in the middle bile duct, and the upstream bile ducts were slightly dilated. In addition, continuous thickening of the bile duct wall from the gallbladder to the confluence of the cystic duct was observed. No distant metastases, such as liver metastases, or nearby enlarged lymph nodes were observed (Fig. 1). Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography revealed a papillary-like elevated lesion in the bile duct around the confluence of the cystic duct (Fig. 2). However, a subsequent biliary biopsy for histology and biliary

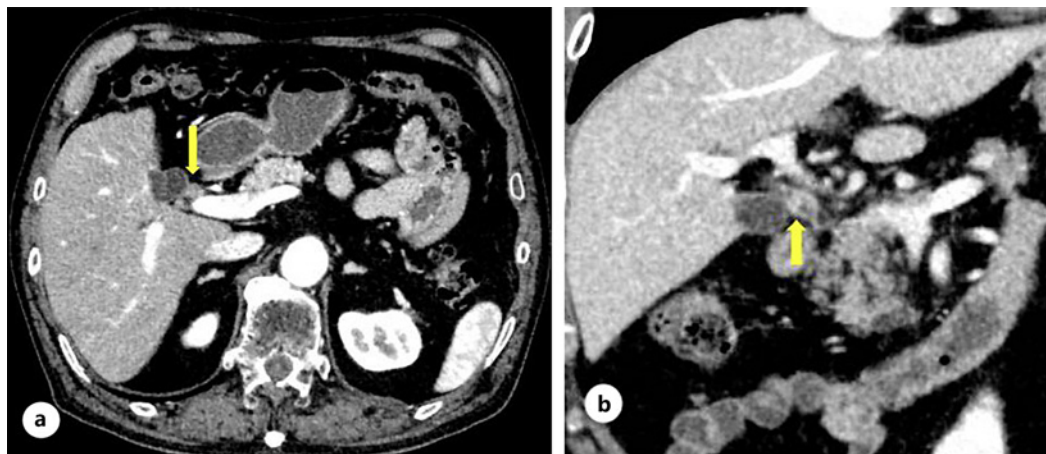


Fig. 1. a, b Contrast-enhanced computed tomography showed localized wall thickening in the middle bile duct, and the upstream bile ducts were slightly dilated. In addition, there was continuous thickening of the bile duct wall from the gallbladder to the confluence of the cystic duct. No distant metastasis, such as liver metastasis or nearby enlarged lymph nodes, was observed.

brushing for cytology from the same area showed no malignant findings. Endoscopic ultrasonography showed irregular thickening of the gallbladder wall and a contiguous tumor from the gallbladder to the cystic duct (Fig. 3).

Given the above, the possibility that the patient had a gallbladder or bile duct neoplasm, including intraductal papillary neoplasm of bile duct (IPNB), could not be ruled out. Therefore, we decided to perform surgery with the ascending colon tumor after obtaining sufficient informed consent from the patient.

Extrahepatic bile duct resection and right hemicolectomy were performed. During laparotomy, no liver metastasis or peritoneal dissemination was observed. First, pancreaticoduodenal mobilization was performed, and lymph node #13 was dissected. In addition, the intrapancreatic bile duct was dissected and the distal bile duct margin was subjected to a fast frozen section analysis, which showed negative results for a malignant neoplasm. The hepatoduodenal ligament was dissected, and the bile duct margin on the hilar side was near the bifurcation of the right and left hepatic ducts, which was also found to be negative for malignancy by a fast frozen section analysis. The atrophied gallbladder was firmly adherent to the right hepatic duct and difficult to detach. After extrahepatic bile duct resection, biliary reconstruction was performed via Roux-en-Y hepaticojejunostomy.

A gross examination of the resected specimen revealed severe atrophy of the gallbladder and polypoid lesions in the bile duct (Fig. 4). A histopathological examination of the resected specimen revealed hyperplasia of the accessory glands in the bile ducts from the cystic duct to the confluence of the cystic duct, with proliferation of the small glandular ducts within the polypoid lesion, which retained the lobular structure without dysplasia (Fig. 5). Furthermore, this mass was not mucus-secreting. The Ki-67 labeling index was <1%. The ratio of IgG4-positive to IgG-positive plasma cells was approximately 10%, and the presence of IgG4-related disease was ruled out, including findings of serum IgG4 levels. The gallbladder showed fibrosis in all layers of the wall, and there was no obliterative phlebitis or storiform fibrosis, which are characteristics of IgG4-related diseases, suggesting fibrous wall thickening due to chronic cholecystitis. Based on the above findings, this case was considered to be one of peribiliary gland hyperplasia with chronic inflammatory cell infiltration and fibrosis.

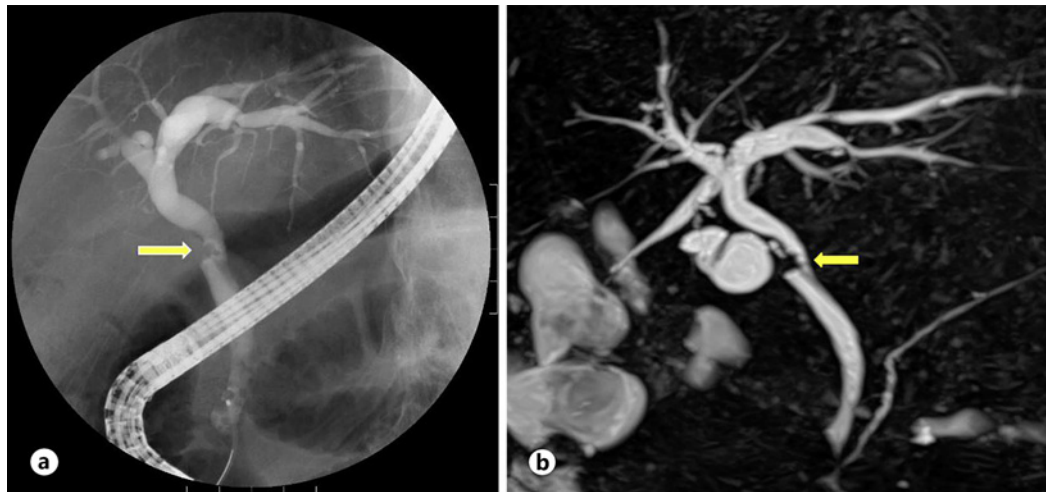


Fig. 2. **a, b** Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography revealed that a papillary-like elevated lesion in the bile duct around the confluence of the cystic duct. A subsequent biliary biopsy and biliary brushing from the same area showed no malignant findings.

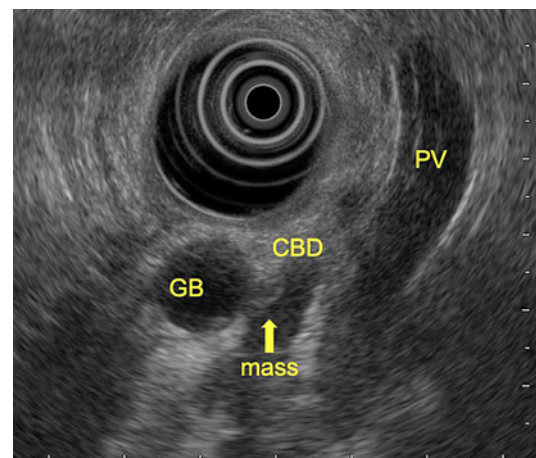


Fig. 3. Endoscopic ultrasonography showed irregular thickening of the gallbladder wall and a tumor contiguous from the gallbladder to the cystic duct.

Discussion

Peribiliary glands are glandular tissues found in extrahepatic bile ducts and large intrahepatic bile ducts (e.g., right and left hepatic ducts and regional branches) [1–3]. They are also known as the Beale ducts, Beale glands, deep glands, biliary glands, periductal glands, and extrahepatic peribiliary glands [4]. Peribiliary glands are abundant near the porta hepatis and duodenal papilla and are densely distributed in the cystic duct. These glands are classified into intramural (within the bile duct wall) and extramural (outside the bile duct wall with sparse connective tissue) glands [2]. Intramural glands are tubular mucous glands that open directly into the lumen of the bile duct lumen. The extramural glands are lobular, mixed glands composed of mucous and serous glands that drain into the bile duct lumen via a unique conduit. Extramural glands rarely contain pancreatic exocrine glands, which are of interest in terms of biliary and pancreatic tumorigenesis. Indeed, it has been reported that IPNB arising in the peribiliary glands may be a counterpart of branched intraductal papillary mucinous neoplasm [5, 6].

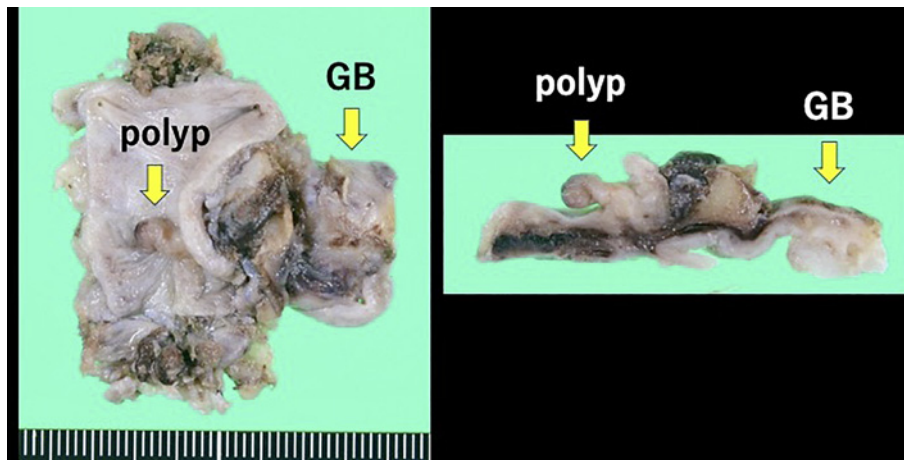


Fig. 4. A gross examination of the resected specimen revealed severe atrophy of the gallbladder and polypoid lesions in the bile ducts.

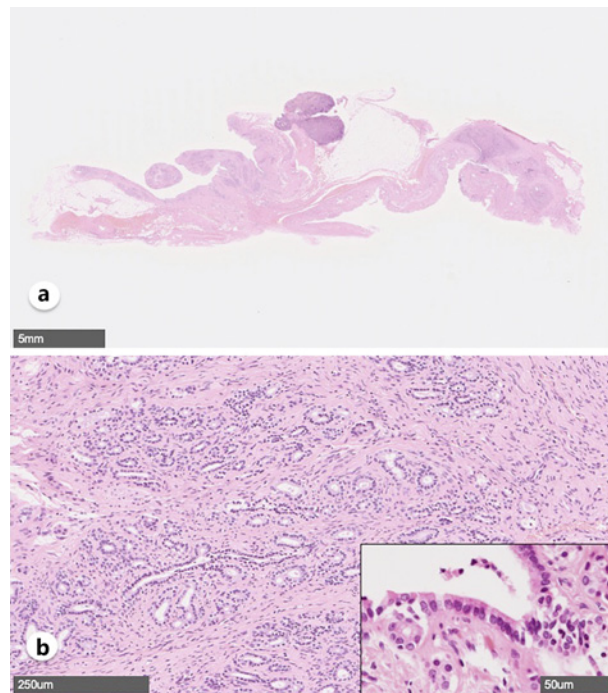
Tissue stem cells and progenitor cells are known to be responsible for tissue regeneration when tissues are damaged by external stimuli, such as inflammation, and tissue repair by these cells is observed mainly in the regeneration of rapidly metabolizing tissues, such as the epithelium of the digestive tract and skin [7]. Although the existence of peribiliary glands has been known for some time, little attention has been paid to their significance. However, recent reports have revealed that tissue stem cell markers are highly expressed in the peribiliary glands [8]. Based on these findings, peribiliary glands appear to be tissue stem cells involved in bile duct tissue regeneration. In the present case, chronic inflammation due to cholecystitis was present, and it is possible that the growth of the peribiliary glands occurred as part of tissue regeneration in response to tissue damage caused by inflammation.

In the present case, preoperative computed tomography showed thickening of the bile duct wall due to proliferation of this peribiliary gland, which resembled cholangiocarcinoma. A histopathological examination of the lesion in this case revealed hyperplasia of the small glands without atypia. The lobular structure was preserved, and the lesion was covered by flat biliary epithelia. Gallbladder adenomyomatosis is characterized by gallbladder wall thickening containing bile-filled cystic spaces and hypertrophy of the muscles around them. In this case, neither Rokitansky-Aschoff sinus-like structures with bile secretion nor muscle hypertrophy were observed, so gallbladder adenomyomatosis was ruled out. Furthermore, papillary epithelial lesion was not detected by a histopathological examination, excluding the possibility of IPNB, BilIN, or cystic micropapillary neoplasm of peribiliary glands. Pyloric gland adenoma (PGA) of the gallbladder is a polypoid, preinvasive epithelial neoplasm. Histological differentiation between PGA and peribiliary hyperplasia might be difficult, as both PGA and peribiliary glands present a similar morphology and express MUC6. However, PGA is often accompanied by a foveolar epithelial component, which conflicted with the present findings.

Differentiation from IgG4-related disease was problematic in the present case, but since there was no evidence of obliterative phlebitis or storiform fibrosis, and the IgG4/IgG expression ratio was approximately 10% (compared to more than 40% for IgG4-related disease), IgG4-related disease was considered histologically negative.

The sensitivity of brush cytology and biopsies in bile duct cancer is reported to be approximately 30–60% and 40–60%, respectively, and the pathological diagnosis of a negative result is problematic for differentiation from other diseases [9]. Diseases that can be

Fig. 5. a, b A histopathological examination of the resected specimen revealed that hyperplasia of the accessory glands of the bile ducts, with proliferation of the small glandular ducts within the polypoid lesion, which retained a lobular structure with little atypia.



differentiated from bile duct cancer include sclerosing cholangitis, multiple biliary papillomatosis, granulosa cell tumors, neuroendocrine tumors, neural tumors, heterotopic tissue, and extrahepatic biliary tuberculosis [10]. Bile duct cancer requires relatively invasive surgery such as pancreaticoduodenectomy or major hepatectomy, which is clearly overly invasive for these diseases. In the present case, we performed an intraoperative fast frozen section analysis and found no evidence of malignancy. As a result, extrahepatic bile duct resection with major hepatectomy, the standard procedure for bile duct cancer at this site, was able to be avoided.

Conclusions

We encountered a case of peribiliary gland hyperplasia that was difficult to differentiate from bile duct cancer. In recent years, the diagnostic ability has dramatically increased with improvements in the image quality and peroral cholangioscopy operability and the development of new treatment tools. We hope that these advances and the ability to perform a preoperative examination of the pathophysiology of this disease will facilitate an accurate preoperative diagnosis of peribiliary gland hyperplasia in the future. The CARE Checklist has been completed by the authors of this case report, and it is attached as supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000538491>).

Statement of Ethics

This case report was approved by the Institutional Review Board of Tohoku Medical and Pharmaceutical University Hospital, approved number: 2023-4-010. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

There is no funding related to this research.

Author Contributions

Kazuhiro Takami, Kuniharu Yamamoto, Hiroto Sakurai, Noriko Kondo, and Yu Katayose were involved in study design and data interpretation. Kuniharu Yamamoto, Hiroto Sakurai, Yoshihiro Sato, Noriko Kondo, Toru Nakano, Shingo Tsujinaka, Akinobu Koiwai, Morihisa Hirota, Keigo Murakami, Kazuhiro Murakami, Chikashi Shibata, and Yu Katayose critically revised the manuscript, commented on drafts of the manuscript, and approved the final report.

Data Availability Statement

The data supporting the findings of this study are available upon request from the corresponding author. Data are not available to the public because they contain information that may violate the privacy of the study participants.

References

- 1 Terada T, Nakanuma Y, Ohta G. Glandular elements around the intrahepatic bile ducts in man; their morphology and distribution in normal livers. *Liver*. 1987;7:1–8. <https://doi.org/10.1111/j.1600-0676.1987.tb00308.x>.
- 2 Terada T, Nakanuma Y. Innervation of intrahepatic bile ducts and peribiliary glands in normal human livers, extrahepatic biliary obstruction and hepatolithiasis. An immunohistochemical study. *J Hepatol*. 1989;9(2): 141–8. [https://doi.org/10.1016/0168-8278\(89\)90044-5](https://doi.org/10.1016/0168-8278(89)90044-5).
- 3 Nakanuma Y, Zen Y, Portman BC. Diseases of the bile ducts. In: Burt AD, Portman BC, Ferrell LD, editors. *MacSween's pathology of the liver*. 6th ed. Livingstone: Churchill; 2011.
- 4 Segamalai D, Lakshmanan A, Jameel ARA, Chandrabapulu S, Gounder KD. Benign Beale gland hyperplasia mimicking malignant biliary obstruction. *J Clin Diagn Res*. 2017;11(7):10–1. <https://doi.org/10.7860/JCDR/2017/26242.10157>.
- 5 Adsay NV, Fukushima N, Furukawa T. Intraductal neoplasms of the pancreas. In: Bosman FT, Carnerio F, Hruban RH, Theise ND, editors. *WHO classification of tumors of the digestive system*. 4th ed. Lyon: IARC Press; 2010.
- 6 Lim JH, Zen Y, Jang KT, Kim YK, Nakanuma Y. Cyst-forming intraductal papillary neoplasm of the bile ducts: description of imaging and pathologic aspects. *AJR Am J Roentgenol*. 2011;197(5):1111–20. <https://doi.org/10.2214/AJR.10.6363>.
- 7 Mills JC, Shivdasani RA. Gastric epithelial stem cells. *Gastroenterology*. 2011;140(2):412–24. <https://doi.org/10.1053/j.gastro.2010.12.001>.
- 8 Wang Y, Lanzoni G, Carpino G, Cui CB, Dominguez-Bendala J, Wauthier E, et al. Biliary tree stem cells, precursors to pancreatic committed progenitors: evidence for possible life-long pancreatic organogenesis. *Stem Cell*. 2013;31(9):1966–79. <https://doi.org/10.1002/stem.1460>.
- 9 Weber A, von Weyhern C, Fend F, Schneider J, Neu B, Meining A, et al. Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. *World J Gastroenterol*. 2008;14(7):1097–101. <https://doi.org/10.3748/wjg.14.1097>.
- 10 Inal M, Aksungur E, Akgul E, Demirbas O, Oguz M, Erkocak E. Biliary tuberculosis mimicking cholangiocarcinoma: treatment with metallic biliary endoprosthesis. *Am J Gastroenterol*. 2000;95(4):1069–71. <https://doi.org/10.1111/j.1572-0241.2000.01944.x>.