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Spontaneous necrosis of gallbladder carcinoma in patient with pancreaticobiliary maljunction

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Abstract While gallbladder carcinoma is occasionally associated with pancreaticobiliary maljunction, spontaneous necrosis of carcinoma is extremely rare. We herein present a case of spontaneous necrosis of gallbladder carcinoma associated with direct invasion of viable cancer cell nests to the muscularis propria and subserosal layer located beneath the primary nodules. A 65-year-old Japanese man was admitted to a local hospital, complaining of repeated discomfort in the right hypochondrium. Ultrasonography and computed tomography scanning revealed cholecystitis associated with gallstones. Cholecystectomy was performed, and operative cholangiography demonstrated pancreaticobiliary maljunction. The resected gallbladder showed multiple mixed stones filled with necrotic debris and bile sludge. Scrutiny of the mucosal surface revealed multiple small necrotic nodules in the fundus, which were histologically confirmed to be necrotic remnants of a cancerous glandular structure. Small nests of papillary adenocarcinoma were found beneath the nodules in the muscularis propria and in the venous structure located in the connective tissues next to the divided margin of the gallbladder bed. Resection of S4a and S5 of the liver and resection of the extrahepatic bile duct was then performed to remove the remaining cancerous tissues and/or micrometastasis in the liver and bile duct. The biliary tree was reconstructed with a hepaticoduodenostomy. No cancer nests or any precancerous lesions were found in the additionally resected specimens. This case indicates a unique morphological feature of gallbladder carcinoma associated with pancreaticobiliary maljunction, which provides some insight into the pathogenesis of spontaneous necrosis of gallbladder carcinoma.

Key words Gallbladder carcinoma · Pancreaticobiliary maljunction · Spontaneous necrosis

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Introduction

It has been recognized that the overall clinical outcome of gallbladder carcinoma (GBC) is not sufficiently favorable.[1–4] While satisfactory results have been obtained for GBC confined to the mucosa and the muscularis propria,[5,6] the prognosis of advanced carcinoma, where the depth of invasion extends to and beyond the subserosal layer, is still poor.[2,3,6] Although it has been reported that aggressive surgery for advanced GBC has improved prognosis, the morbidity and mortality of the aggressive surgical procedures are sometimes high.[3,7] Thus, precise evaluation of clinical stage and optimal surgery is important to achieve long-term survival.

It has been shown that GBC is often associated with pancreaticobiliary maljunction (PBM); however, the mechanism of the carcinogenesis is not completely understood, and the histopathological characteristics of GBC in PBM should be collected. Here, we describe a case of necrotic GBC associated with pancreaticobiliary maljunction. Although the entire primary nodule was necrotic, tiny cancer cell nests were seen beneath the primary nodules located in the subserosal layer of the gallbladder bed. These morphological features provide an insight into the pathogenesis of the necrotic GBC. The pathogenesis of the carcinoma and the optimal surgical procedure in the present patient are discussed.

Case report

A 65-year-old Japanese man visited a local hospital on March 6, 2000, with complaints of repeated discomfort in the right hypochondrium of 2 years' duration. Ultrasonography (Fig. 1a,b) and computed tomography (CT) scanning (Fig. 2) performed at the local hospital revealed enlargement, thickening of the gallbladder wall, and multiple strong echoes associated with

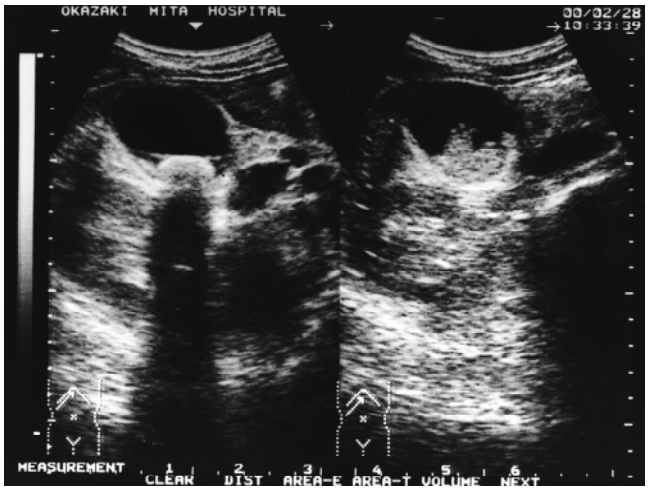


Fig. 1. Abdominal ultrasonography conducted at a local hospital, revealing thick-walled gallbladder associated with multiple gallstones (*left*) and bile sludge (*right*), which was depicted as an irregularly shaped high-echoic mass in the gallbladder

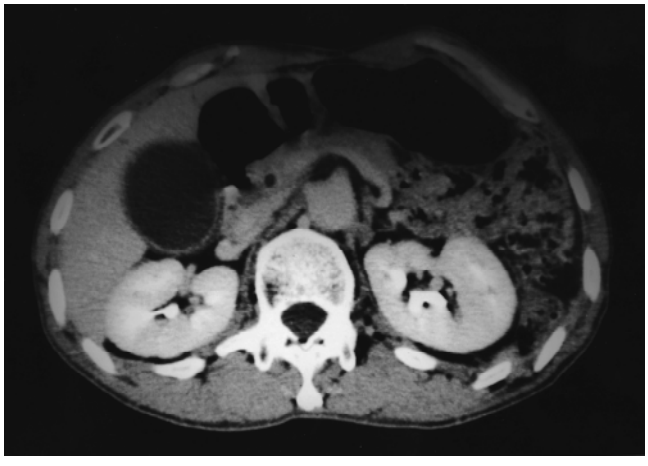


Fig. 2. Computed tomography scanning performed at a local hospital revealed enlargement and thickening of the gallbladder wall

acoustic shadows. An irregular high-echoic area, which was considered to be bile sludge, was also observed in the gallbladder (Fig. 1b). The patient was then referred to our hospital, on March 12, 2000, for an elective cholecystectomy. Laboratory data are shown in Table 1. Endoscopic retrograde cholangiopancreatography (ERCP) revealed dilatation of the extrahepatic bile duct, but the gallbladder was not demonstrated. Precise information regarding the biliary and pancreatic ductal system was not obtained. Laparotomy was performed on March 28, 2000, with a diagnosis of cholecystitis with gallstones. Operative cholangiography demonstrated that the common bile duct was slightly dilated and was 12 mm in size, and the common channel was 15 mm long

Table 1. Laboratory data on admission

Blood chemistry	
Total protein	7.3 g/dl
Albumin	4.0 g/dl
BUN	14 mg/dl
Creatinine	0.5 mg/dl
Total bilirubin	1.7 mg/dl
Direct bilirubin	0.6 mg/dl
AST	11 mU/ml
ALT	8 mU/ml
ALP	28 mU/ml
Cholinesterase	2200 mU/ml
γ-GTP	8 mU/ml
Amylase	83 Units
Na^+	141 mEq/l
K^+	3.8 mEq/l
Cl^-	103 mEq/l
CRP	1.0 mg/dl (0.3 mg/dl)
Blood count	
WBC	11 600 /μl
HGB	13.1 g/dl
RBC	4.15×10^6 /μl
HCT	37.1%
PLT	22.0×10^4 /μl
Tumor markers	
CEA	3.1 ng/ml (5.0 ng/ml)
CA19-9	13.2 U/ml (37 U/ml)

Figures in parenthesis indicate upper limits of the normal range

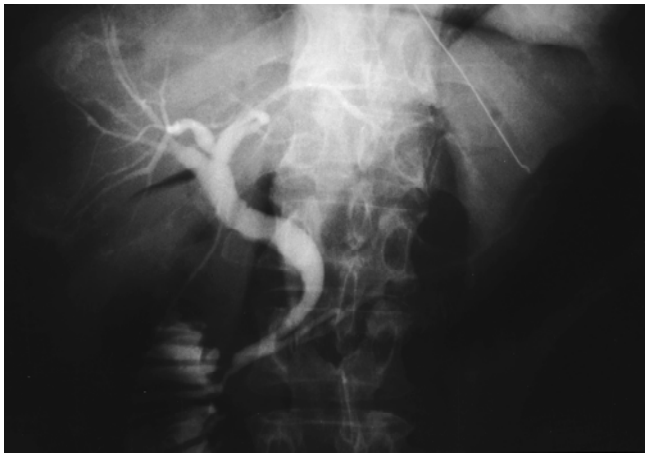


Fig. 3. Operative cholangiography, demonstrating that the common bile duct was slightly dilated and was 12 mm in size, and the common channel was 15 mm long, findings which were compatible with pancreaticobiliary maljunction

(Fig. 3), findings which were compatible with pancreaticobiliary maljunction (PBM) (Fig. 3). Because informed consent regarding reconstruction of the biliary duct had not been obtained, and further examination of the biliary and pancreatic ductal system was considered to be required to determine the presence of biliary carcinoma, simple cholecystectomy alone was performed.

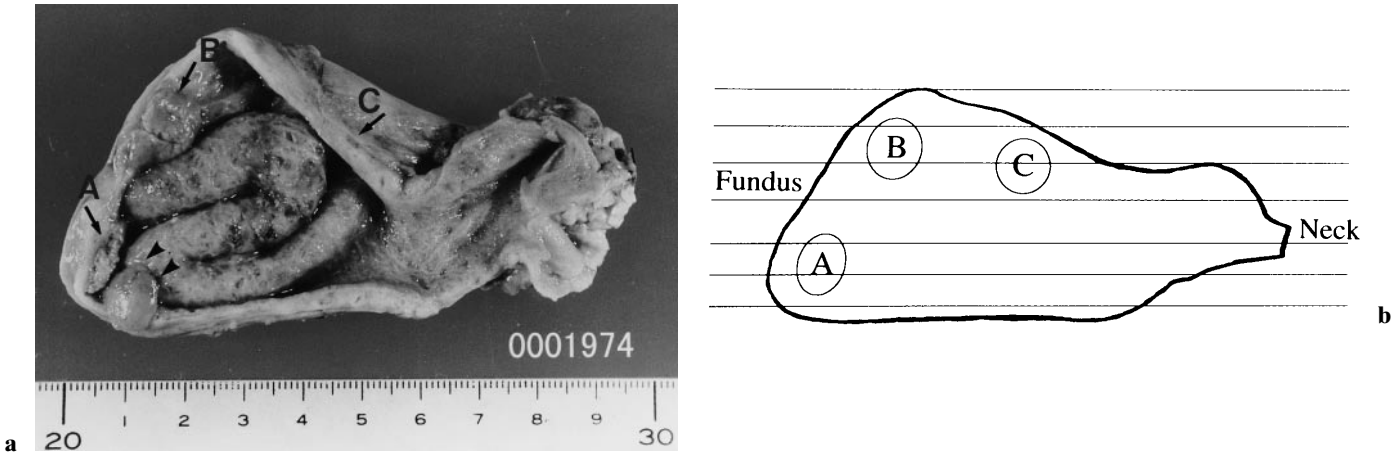


Fig. 4. **a** Macroscopic findings of the resected gallbladder and **b** schematic representation of location of the primary necrotic nodules. Light brown-colored nodules (*arrows indicated as A, B, and C* in **a**) were found in the fundus of the gallbladder. The tip of necrotic nodule A (*arrowheads* in **a**) was artificially detached from its original position. Nodule C is not seen in the photograph, being hidden behind the gallbladder wall

The resected gallbladder had a thick wall and was filled with necrotic debris and multiple mixed stones, one of which was incarcerated in the cystic duct. Scrutiny of the mucosal surface after removal of the debris showed multiple small necrotic nodules of a light-brown color, in the fundus (Fig. 4). Microscopic observation demonstrated a necrotic remnant of a glandular gallbladder structure, with no viable carcinoma cells seen in the area corresponding to the nodular mass (Fig. 5). Reticulin staining of the primary necrotic nodule indicated the presence of reticulum fibers in the stromal tissues extending in a papillary shape (Fig. 6b). Papillary adenocarcinomas that formed small viable cancer cell nests were found in the muscularis propria and in the venous structures located in the loose connective tissues of the subserosal layer next to the divided margin of the gallbladder bed after cholecystectomy. These pathological findings indicated carcinoma of the gallbladder that had directly invaded the muscularis propria and subserosal layer. Necrosis of the carcinoma had occurred only in the primary nodular portion. Obstructed small arteries, associated with the intimal thickening seen in the subserosal layer, were clearly identified by Elastica Van Gieson staining (Fig. 6a). Other portions of the epithelial lining of the mucosal surface of the gallbladder were partially lost because of the poor fixation treatment; however, the epithelial lining was normal, except for the infiltration of inflammatory cells, and no dysplasia or hyperplasia was noted. Although the regional lymph nodes were not dissected during the first operation, the pathological findings indicated t2, N0, H0, P0, M(−) and the patient was staged as stage II according to the "General rules for surgical and pathological studies on cancer of the biliary tract" of the Japanese Society of Biliary Surgery[8] and according to the TNM classification.[9]

Two weeks after the cholecystectomy, ERCP examination reconfirmed the presence of PBM. To pursue complete resection of the GBC, further imaging analyses were performed to determine the extension of carcinoma, such as metastases to the liver and the regional lymph nodes. No evidence suggesting metastasis was obtained. However, considering the possibility of micrometastasis to the gallbladder bed and the regional lymph nodes in the hepatoduodenal ligament, and the possibility of occult carcinoma of the bile duct, partial resection of the liver, regional lymph node dissection, and resection of the extraphepatic bile duct were considered to be required.

On April 18, 2000, resection of S4a and S5 of the liver and the extrahepatic bile duct, and complete skeletonization and dissection of the lymph nodes in the hepatoduodenal ligament were performed. The distal margin of the bile duct was just proximal to the bifurcation of the hepatic duct. No regional lymph node enlargement (nos. 12a, 12p, 12b, 13, 14, 8, 9, and 16) compatible with the metastasis was noted macroscopically. No metastasis to lymph nodes nos. 8, 13, and 16 was found, which was confirmed by examining instant frozen histological sections. Choledochoduodenostomy was performed in an end-to-side fashion. The surgical safety margin of the resected bile duct was also confirmed by examining instant frozen histological sections during the operation.

Complete serial sections, 3-mm-thick, of the resected specimen of the extrahepatic bile duct were prepared for histological examination. Hyperplasia and inflam-

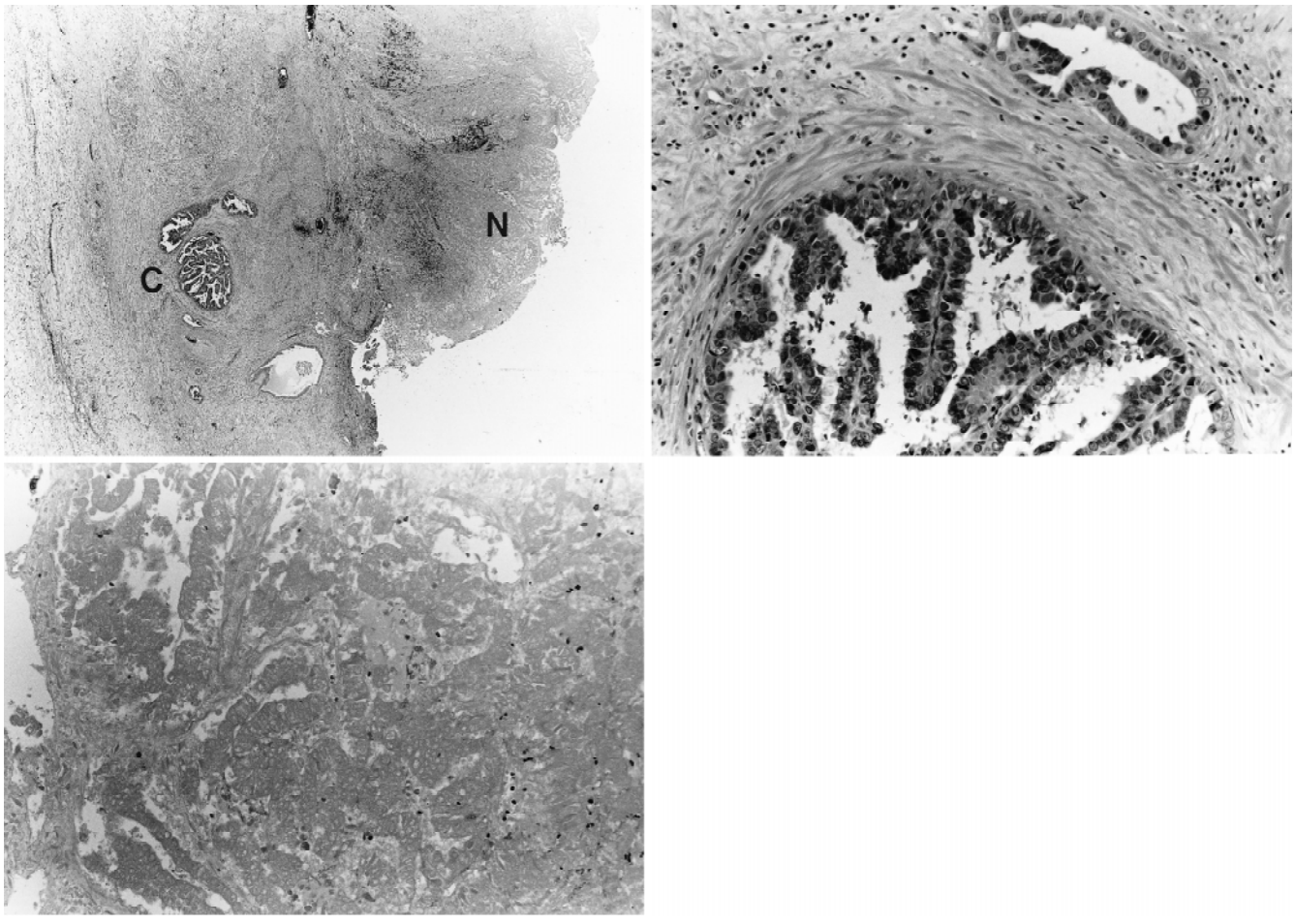


Fig. 5. **a** Low magnification view of necrotic nodule (*N*) protruding toward the luminal surface of the gallbladder, and viable adenocarcinoma (*C*) in the subserosal layer beneath the nodule. **b** Necrotic remnants of glandular structure are shown, with no viable carcinoma cells. **c** Papillary adenocarcinoma which was completely viable, is located in the subserosal layer beneath the nodule. **a** H&E, ×5; **b** and **c** H&E, ×50

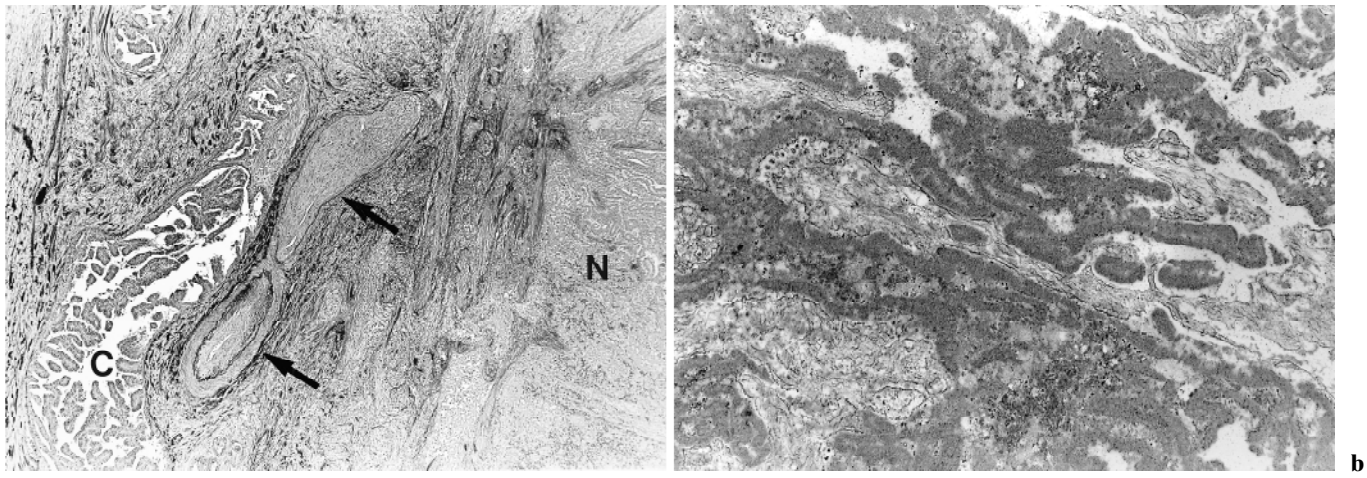
mation were seen in some areas of the bile duct, but no malignant changes or dysplastic lesions were noted in the biliary epithelia. Twenty-five serial microscopic sections of the gallbladder bed were made, to scrutinize the remaining cancer cells, which revealed no cancer cell nests in any of the vessels in the connective tissues. Microscopically, no lymph node metastasis was found in lymph nodes nos. 8, 12, and 13.

The patient's postoperative course was uneventful, except for a minor leakage of the choledochoduodenostomy, and he was discharged on June 14, 2000. He has remained asymptomatic to date.

Discussion

The reasons that our case deserves to be described are twofold: GBC with complete necrosis of the primary nodule has not been documented in the literature, and GBC with a unique morphological feature was associated with the PBM. The primary nodule was completely necrotic; no viable cancer cell was seen in the nodule. A remnant of the glandular structure, consisting of necrotic adenocarcinoma, was a histological feature that could barely be identified in the primary nodules. Beneath the necrotic nodules, viable cancer cell clusters were identified in and beyond the muscularis propria and in the vascular structures. Furthermore, serial histological sections of the entire gallbladder revealed no direct continuance of the necrotic primary nodules with the viable cancer cell cluster located beneath the necrotic primary nodules.

Necrosis of the primary nodules was the most striking pathological finding in the present patient. Three nodules were presented in the fundus and the body of the gallbladder, and all of these nodules were completely necrotic, which was histologically confirmed. In the serial sections of the primary nodules on the luminal



a b

Fig. 6. **a** Elastica Van Gieson staining of the necrotic cancer remnant (*N*) and the viable adenocarcinoma (*C*) in the adjacent subserosal layer, revealing obstructed small arteries associated with intimal thickening (*arrows*). **b** Reticulin staining of the primary necrotic nodule indicated the presence of reticulum fibers in the stromal tissues, extending in a papillary shape

surface of the gallbladder, no viable adenocarcinoma cells were present, and the stromal residue of the well differentiated adenocarcinoma was barely identified by reticulin staining, whereas the portion of the adenocarcinoma that had invaded the muscularis propria and subserosal layer was intact and completely viable. Although the definite cause of the necrosis seen in the primary nodule is still not known, disturbance of the blood flow to the primary nodule is one possible cause. This idea is based on the histological findings, in which obstruction of the small vessels by the cancer cell nests and/or intimal thickening was observed in the adjacent mural structure beneath the nodules. The small arteries in all pathological specimens were examined to determine whether intimal thickening was present in the whole area. It was found that the presence of intimal thickening was limited to the areas adjacent to the invasive carcinoma and/or beneath the necrotic carcinoma. Therefore, the findings of intimal thickening were considered to have no relation to the cholecystitis, but, rather, to be related to the presence of the carcinoma itself. In fact, intimal thickening in the nodular area has been reported in carcinoma of the colon[10] and pancreas,[11] although the etiology of the intimal thickening remains unknown. Nevertheless, intimal thickening may be related to the presence of carcinoma, as well as to the etiology of the spontaneous necrosis. Moreover, there may have been an increase in the intraluminal pressure in the gallbladder, perhaps caused by the incarceration of the stone in the cystic duct, and this may have contributed to disturbance of the blood flow to the primary nodule. This possibility is also supported by the finding of partial loss of the gallbladder epithelia in most mucosal surface areas.

The internal environment inside the gallbladder is another possible mechanism for the necrosis of the primary nodule, because the gallbladder was filled with necrotic debris and bile sludge. Necrosis occurred only in the cancerous lesions that were exposed to the transluminal environment in the gallbladder, which indicates that intraluminal factors may have been involved in the necrosis of the primary nodule. The present patient had cholecystitis, which was confirmed after the cholecystectomy by the finding of the thick gallbladder wall with the infiltration of inflammatory cells and the presence of the debris in the gallbladder. Although no necrotic area of the gallbladder wall, except for the primary nodule, was found, it is possible that the necrosis may have progressed, resulting in gangrenous cholecystitis, if the laparotomy had been delayed. It is well recognized that gangrenous cholecystitis is an ultimate condition resulting from severe forms of cholecystitis. A variety of etiological factors have been postulated for the pathogenesis of gangrenous cholecystitis.[12] Similar mechanisms may have been involved in the necrosis of the primary GBC in the present patient, because high concentrations of pancreatic digestive enzymes have been reported in the biliary ductal system in patients with PBM.[13] However, because the concentrations of pancreatic enzymes in the gallbladder contents were not measured in our patient, whether the presence and activation of pancreatic enzymes were involved in the necrosis of the primary nodule could not be determined.

It has been shown that GBC is often associated with PBM.[14] The database of registered cases of PBM defined by the Japanese Study Group on Pancreaticobiliary Maljunction in 1997 indicated that 14 (9.7%) of 144 cases were associated with GBC. The rate of this

association was significantly higher than that seen in the general population.[15] Great interest has been paid on the high carcinogenic potential of PBM, and mechanisms involved in the frequent association of GBC with PBM have been postulated, such as the chronic irritation of gallbladder epithelium caused by back flow and retention of pancreatic digestive enzymes. These enzymes are then activated by mixing with bile fluid in the gallbladder, and this series of events consequently stimulates mutagenicity.[16] This may cause a favorable environment for carcinogenesis of the gallbladder epithelium. In this regard, the present case provides some insight into the pathogenesis and the clinical features of GBC associated with PBM.

Resection of the extrahepatic bile duct was performed in our patient. We have advocated resection of the extrahepatic bile duct for patients with PBM, regardless of dilatation of the biliary tree.[17] The rationale for the exclusive resection of the extrahepatic duct is based on the high carcinogenic potential of the biliary epithelium in patients with PBM.[15] Furthermore, it has recently been reported that multiple genetic mutations were found in noncancerous lesions in biliary epithelium, regardless of dilatation of the bile duct.[18–21] Furthermore, biliary reconstruction using an end-to-side choledochoduodenostomy has been shown to be adequate, because it provides a simple and physiological route for the outflow of bile fluid.[22]

In summary, the present case demonstrated unique morphological features of GBC associated with PBM. Although the relationship of PBM itself to the etiology of the necrotic adenocarcinoma is considered to be unlikely, spontaneous necrosis of gallbladder carcinoma is extremely rare, and this case may provide an insight into the pathogenesis of spontaneous necrosis of primary adenocarcinoma.

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