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症 例

Adenocarcinoma in Papillomatosis of the Gallbladder: A Case Report

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Only a few cases of papillomatosis of the gallbladder have been described in the literature. GRAZIANI reported a 21-year-old male who had innumerable papillary projections measured up to 1 cm in length and occupied most of the mucosal surface of the gallbladder¹⁰⁾. ALMAGRO reported a 62-year-old male who had papillary excrescences in the entire mucosa of the gallbladder²⁾. Histologically, these tumors has been reported to be of benign, and composed of a single layer of columnar epithelial cells with basal nuclei lining thin connective tissue stalks^{10, 2)}.

Similar lesions of the biliary tract other than the gallbladder have more frequently been reported^{6, 7)}. It is noteworthy that these lesions of the bile duct often recurred irrespective of primary focus resection^{1, 9, 12)}. NEUMANN reported recurrent papillomatosis of the bile duct, and observed marked epithelial atypia in the papillary neoplasms of surgically resected bile duct, and some cancerous foci infiltrating into the periductular organs at autopsy¹³⁾.

We encountered a case papillomatosis in the cholecystectomized gallbladder of a 42-year-old male in who abdominal carcinomatosis developed 4 and a half years after cholecystectomy.

Case History

An obese 42-year-old male first visited our hospital complaining of colic epigastralgia with nausea and recurrent vomiting for 3 days. Tenderness at the upper right quadrant of the abdomen was noted. The initial laboratory evaluations included leukocytosis, increase of the value of serum bilirubin value and normal routine roentgenographic findings. Further image studies were performed after subsidence of acute inflammatory state following administration of antibiotics.

Intravenous cholangiography and ERCP showed common bile duct dilation up to 25 mm in

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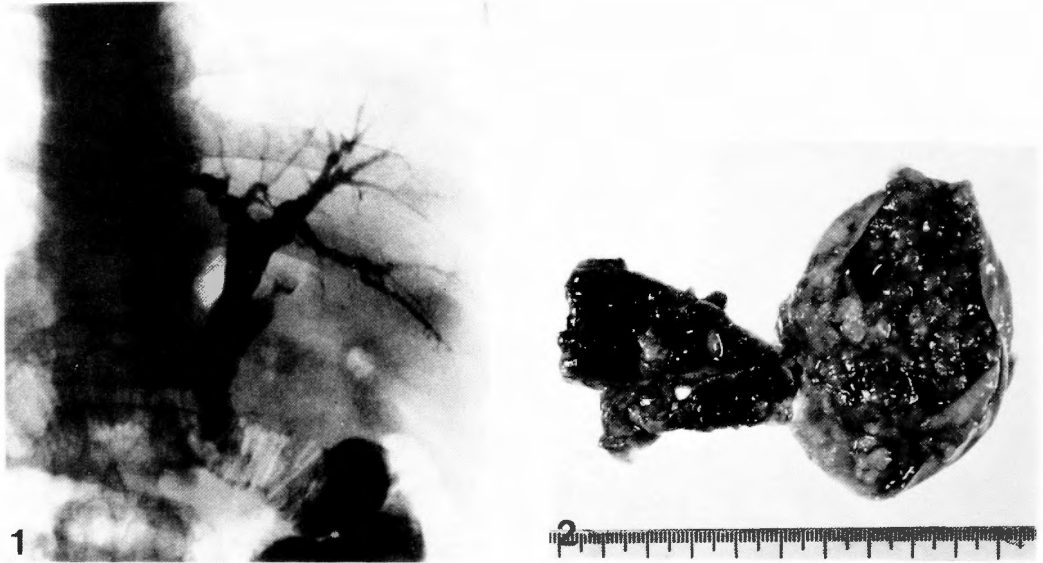


Fig. 1. The picture of ERCP before the operation. Dilation of the common bile duct is noted and the gallbladder is not filled by contrast medium.

Fig. 2. Resected gallbladder. Almost the entire mucosa was occupied by innumerable friable tumors.

diameter and the gallbladder was not filled with contrast medium (Fig. 1). The patient was operated on under the diagnosis of cholelithiasis.

Laparotomy revealed the severely distended gallbladder and some small necrotic foci in the pancreas. In the process of removing the gallbladder, its cervical wall was accidentally ruptured and many small soft tumors with mucinous fluid entered the peritoneal cavity. As many of these tumors as possible were removed from the peritoneal cavity by washing with saline. Exploration of the common bile duct revealed intact mucosa. No stone was found. A T-tube was inserted into the common bile duct before the closure of the peritoneum.

The resected gallbladder was 9×6 cm with slight thickening of the wall. Innumerable small papillary neoplasms occupied almost the whole gallbladder mucosa (Fig. 2). Each tumor were sessile, friable, from 0.5 to 1.0 cm in diameter, and reddish-brown in color. Some of the tumors easily detached from the mucosa, and floated in the mucinous fluid.

The tumors were principally composed of vascularized fibrous tissue lined with regularly arranged cuboidal or columnar epithelial cells on the initial histological examination. Retrospective inspection by multiple sections of the gallbladder revealed a few small atypical foci presenting back to back structure of the glands or pseudostratified atypical epithelial cells at the free surface of the tumors (Fig. a). Subsequent cholangiography through the T-tube showed no stenosis or filling defect, he was discharged on the 27th postoperative day.

The patient had been asymptomatic for about 4 and a half years after the operation. Then, he felt general fatigue, which often prevented him from working. Because of right hypochondralgia and abdominal fullness, he visited local physician who found massive ascites accumulation. He was readmitted to our hospital under the diagnosis of liver cirrhosis.



Fig. 3. One of the tumor attached to the peritoneum with mucinous secretory material removed at autopsy.

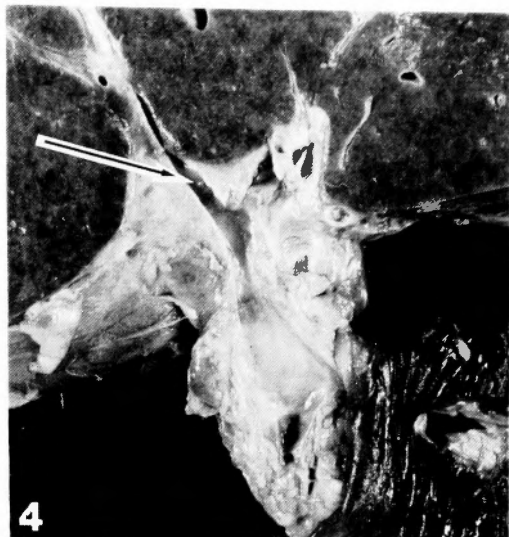


Fig. 4. A small friable tumor (arrow) was located in the dilated intrahepatic bile duct.

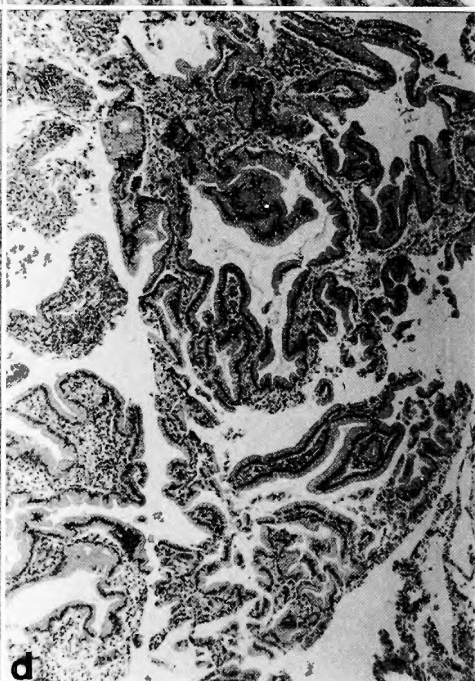
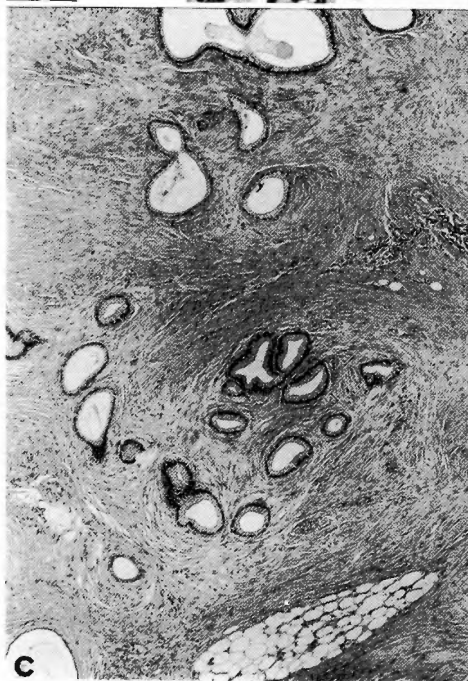
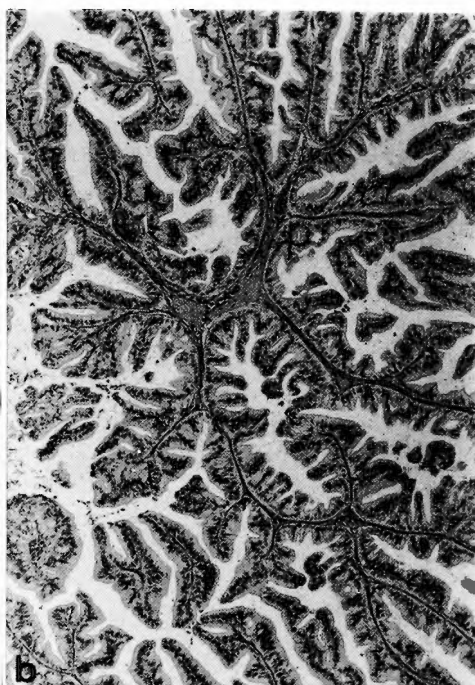
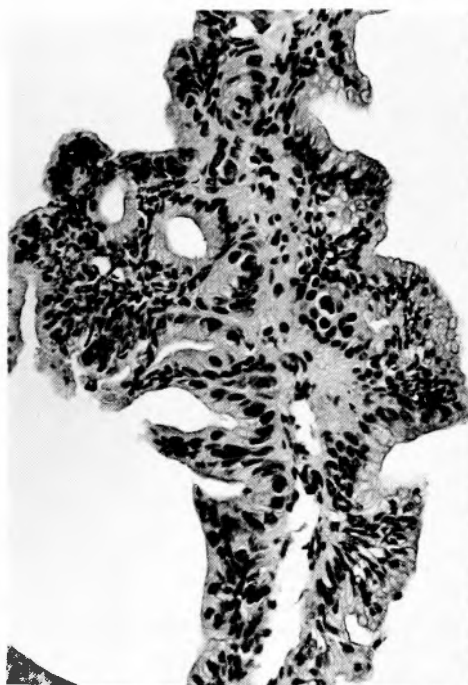
The initial laboratory data included increase in serum GOT, GPT and r-GTP, but normal bilirubin values. Frequent paracentesis finally revealed bloody ascites containing cytologically malignant cells originated from adenocarcinoma. Further extensive image studies, upper GI series, barium enema, endoscopy and arteriography disclosed no primary focus. ERCP showed a small filling defect in the intrahepatic bile duct.

Combination chemotherapy consisted of Adriamycin, 5-Fu, Mitomycin-C and OK-432 was performed. Ascites became clear (no blood) and decreased in volume. However, paralytic ileus appeared with massive fluid discharge from the gastric tube. The patient died 5 months after the second admission, and it was 5 years after the first operation.

Autopsy findings: Multiple papillary tumors were disseminated in the peritoneum. These tumors were hard and grayish-white in color, and most of them only attached to the peritoneum by mucin (Fig. 3). Some tumors fibrously adhered to the peritoneum by cancerous infiltration. All of these tumors were histologically well-differentiated adenocarcinoma (Fig. b). At the part where the tumors fixed to the peritoneum, infiltrative proliferation of tubular epithelial cells with prominent fibrosis was seen (Fig. c). Despite of these intraperitoneal metastatic tumors, there was no cancerous lesion in any organs except the peritoneum. Abdominal lymph nodes were also intact.

A friable tumor, 0.5×0.2 cm in size, was found in the dilated bile duct (Fig. 4). Histologically, it showed typical features of papilloma (Fig. d). The large and small intestines had degenerative or necrotic mucosa, adhered to each other.

Hemorrhagic foci were found in the following organs: pericardium, pleura, lungs, pelvic mucosa of the kidneys, conjunctiva and the skin on both lateral sides of the abdomen.



Discussion

Distinct macroscopical aspects of the present tumors, being in accordance with the previous descriptions of biliary papillomatosis, assured of its belonging to the rare entity. Although almost all of the tumors were histologically less atypical, tiny cancerous lesions were found at the free surface of the tumor without submucosal invasion. The postmortem examination revealed the condition of abdominal carcinomatosis without cancerous lesions thought to be primary foci. The tumors in the peritoneum were histologically well-differentiated adenocarcinoma. These findings suggested that the gallbladder tumors recurred in the peritoneum.

The mode of recurrence of the present case differs from that of carcinoma of the gallbladder. First, a long asymptomatic period from the operation to the recurrence is exceptional in gallbladder carcinoma of which the prognosis is poor with a 5-year survival rate of 4 to 7%^{14,15}. In addition, tumor spreading in the present case differs from that of gallbladder carcinoma. Extensive intraperitoneal spreading of tumors occurred without lymph node involvement or vascular spreading. Furthermore, the biliary tract was intact even at autopsy. In contrast, intraperitoneal spreading of carcinoma of the gallbladder usually takes the form of involvement of adjacent viscera^{5,8}, or leads initially to focal invasion of the liver, stomach or duodenum.¹¹ In view of the discrepancy between little involvement of the organs adjacent to the gallbladder and the vast metastatic lesions in the peritoneum, the dissemination of tumors to the peritoneum was considered to occur directly from the primary focus in the gallbladder, which was simultaneously resected without tumor residue in the bile duct. Consequently, the accidental scattering of tumors from the ruptured gallbladder during the first operation was the most probably way of tumor spreading.

This consequence indicates the distinct biological nature of papillomatosis of the gallbladder, that is, a long latent malignant nature as demonstrated by its slow growth within the peritoneum for 4.5 years, which finally resulted in massive accumulation of ascites. A long latent malignant nature has also been reported as a distinct feature on recurrent papillomatosis of the bile duct, and the involved sites were limited to the biliary tract or adjacent organs^{1,9,12,13}.

At autopsy, a papilloma was found in the intrahepatic bile duct. This substantiated the recurrence of papillomatosis of the gallbladder in the bile duct irrespective of cholecystectomy; this recurrence may eventually cause fatal bile duct obstruction.

In the present case, colic epigastralgia, jaundice and bile duct dilation appearing without bile duct involvement by tumors was remarkable. Papillomas in the non-carcinomatous gallbladder has frequently been noted to be accompanied by symptoms identical to an attack of acute cho-

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- Fig. a.** High magnification picture of atypical lesion of the tumor. Pseudostratification of nuclei, loss of nuclear polarity and back to back structure of the gland is noted ($\times 760$, H.E. stain).
- Fig. b.** Histological feature of the tumor in the peritoneum was extremely well-differentiated adenocarcinoma ($\times 175$, H.E. stain).
- Fig. c.** Histological feature of the tumor infiltrated into the omentum. Infiltration of tubular epithelial cells with prominent fibrosis is seen ($\times 175$, H.E. stain).
- Fig. d.** Histological feature of the tumor found in the intrahepatic bile duct. Typical feature of papilloma is seen ($\times 175$, H.E. stain).

lecystitis and gallstones^{3,11)}. In a patient with papillomatosis of the gallbladder accompanied by intermittent epigastric pain and vomiting, the obstruction of the cystic duct and/or common bile duct by fragment of papilloma, blood clots or both, was suspected to be the cause of these symptoms¹⁰⁾. In the present case, the symptoms probably resulted from the obstruction of bile duct by detached tumors or mucinous fluids passing through the cystic duct.

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和文抄録

癌性腹膜炎に進展した胆嚢 papillomatosis の一例

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胆嚢結石症の診断で手術を施行した患者で, 胆嚢粘膜全体が無数の柔らかい乳頭状の腫瘍で占められているのが発見された。組織学的には, 表層の一部に癌性病巣のみられる乳頭腫様の像を呈していた。術中に胆

嚢を穿破し, 胆嚢内の腫瘍が腹膜内に散布された。術後5年に癌性腹膜炎で死亡した。剖検で高分化型腺癌の腹膜播腫と乳頭腫の胆管再発がみられた。