

A Clinicopathological Study of Unsuspected Carcinoma of the Gallbladder

We investigated the incidence of unsuspected gallbladder (GB) carcinomas in a total of 527 consecutive GB specimens resected for benign biliary disease and their clinicopathological features. The GBs were examined microscopically using stepwise tissue sections at 5 mm interval. Clinical and pathological findings were analysed in the cases of unsuspected carcinoma. The 527 patients included 314 women and 213 men (mean age 56.1 years). The incidence of unsuspected GB carcinomas detected during or after cholecystectomy was 1.89%. In ten patients with unsuspected carcinomas, symptoms and signs were nonspecific. Abdominal US showed GB stones (8), thickening of GB wall (1), empyema (2) and a polyp (1). Macroscopically, infiltrative type was the most common. Microscopic examination showed tubular adenocarcinoma. Carcinoma was confined to the mucosa or muscularis (early carcinoma) in 5 cases (50%). The prognosis was good in the patients with early carcinoma, but very bad in advanced cases. In conclusion, unsuspected GB carcinoma was incidentally found in 1.89% of GBs removed for benign biliary disease and a considerable number of these unsuspected cases have an early carcinoma.

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INTRODUCTION

Gallbladder (GB) cancer is a relatively uncommon malignancy of the gastrointestinal tract in Korea (1). The prognosis of GB carcinoma is very poor with less than 5% of 5-year survival rate (2-5). Diagnosis of GB carcinoma is difficult at an early stage because of a lack of specific signs and symptoms. Although diagnosis of GB carcinoma has been improved with the progress in imaging techniques, the diagnostic value of preoperative ultrasound (US), computed tomography (CT), and cholangiography is still limited (5-8).

It has been reported that 10-40% of GB carcinoma was detected incidentally after cholecystectomy (5-7, 9). GB carcinoma was also found in 1-2% of GBs removed for presumed benign biliary disease (7, 10). Long-term survival is expected in patients with unsuspected GB carcinoma, but the prognosis is not uniformly good (9, 11, 12).

The purpose of this study was to demonstrate the clinicopathological features and outcomes of the cases with unsuspected carcinoma of the GB.

MATERIALS AND METHODS

During the years 1990 to 1996, 580 consecutive cholecystectomy specimens were examined pathologically. Unsuspected GB carcinoma is defined as GB carcinoma that is not suspicious preoperatively. The 12 cases of GB cancer diagnosed preoperatively and 41 cases with radical resections for other tumors were excluded. The 527 patients included 314 women and 213 men. The mean age was 56.1 years (S.D. 12.6 years) with a range from 21 to 92 years.

The resected GBs were examined using stepwise tissue sections at 5 mm intervals with mapping. All sections were examined microscopically with hematoxylin and eosin stain. The cases of carcinoma were classified grossly into papillary, nodular, papillary infiltrative, nodular infiltrative, infiltrative, replete, massive and specific types according to the Japanese General Rules for Cancer of the Biliary Tract (13). The tumors were staged according to Nevin's classification as follows : stage I, intramucosal involvement only; stage II, involvement of mucosa and muscularis; stage III, transmural involvement; stage IV,

transmural and cystic lymph node involvement; stage V, contiguous or metastatic liver involvement or distant metastases (2).

The patients with GB carcinoma were followed up until death or December 1996.

RESULTS

Table 1 shows the presumed diagnosis before the operation in 527 patients. Gallstones were found in 387 cases (73.4%). GB carcinoma was found incidentally during or after cholecystectomy in 10 cases (1.89%).

The ten patients with unsuspected GB carcinoma included 7 women and 3 men and their mean age was 68.1 years ranging from 52 to 82 years. The most common presenting symptom was abdominal pain (10 cases) and the other symptoms were jaundice (4 cases), fever (2 cases) and weight loss (3 cases). Hyperbilirubinemia was

present in 5 cases and transaminase was elevated in 6 cases.

Abdominal US showed solitary or multiple stones in eight patients, thickening of the GB wall in 1, polyp in 1, GB empyema in 2, common bile duct stones in 2 and ascites in 2 patients. Abdominal US could not be performed in one case having an emergency operation for peritonitis. Preoperative diagnoses in the cases with unsuspected GB carcinoma are given in Table 2.

Operative cholecystectomy alone was performed in all patients. GB carcinoma was diagnosed in 2 cases (case 9, 10) during the emergency operation by the findings of GB perforation with metastasis to adjacent organs.

Macroscopically, infiltrative type was the most common. No definite tumor mass was grossly identified in 50% of the cases of unsuspected GB carcinoma. Microscopic examination showed well differentiated tubular adenocarcinoma in 8 cases and moderately differentiated tubular adenocarcinoma in 2 cases.

Carcinoma was confined to the mucosa in two patients (stage I), extended into the muscularis in three (stage II), and involved the entire thickness of the GB wall in three (stage III). Invasion of the liver or lymph node metastasis was found in two cases (stage V) according to Nevin's classification. Lymphatic or vascular invasion was seen in all cases of advanced stages (III, V), but none of the early GB carcinoma (stage I, II) showed invasion of lymphatics, veins or perineurium. In case 2, the mucosa showed diffuse dysplastic change with multifocal transformation of the carcinoma (Table 2).

The mean duration of follow-up was 2 years (5 months-6 years). Four of five patients with early carcinoma have been doing well after the operation. Most of the patients with advanced stage died within 6 months postoperatively.

Table 1. Indications for Cholecystectomy in Total 527 Cases

Indication	No. cases
Cholecystitis	446 (84.6%)
GB empyema	25 (4.7%)
Cholangitis	12 (2.3%)
GB polyp	10 (1.9%)
IHD stone	10 (1.9%)
Choledochal cyst	5 (0.9%)
Biliary-enteric fistula	3 (0.6%)
Porcelain GB	1 (0.2%)
Adenomyomatosis	1 (0.2%)
Other benign dis.*	14 (2.7%)

* Incidental cholecystectomy during operation for benign diseases of gastrointestinal tracts or traumatic injury.

Table 2. Clinico-pathological Findings of the 10 Cases with Unsuspected GB Carcinoma

Case	Age (Yr.)	Sex	Preop. diagnosis	Gross type*	Location	Size (cm)**	Microscopic finding	Stage (Nevin)	Follow-up
1	61	F	GB polyp	Nodular	Fundus	1.2	Adenoca. well	I	6yr. alive
2	71	M	Cholangitis	Infilt.	Entire	8.3	Adenoca. well	I	3yr. alive
3	64	F	Cholecystitis	Infilt.	Body	4.0	Adenoca. well	II	2yr. alive
4	58	F	Cholecystitis	Infilt.	Body	1.4	Adenoca. well	II	2yr. alive
5	69	M	GB stone	Infilt.	Fundus	1.8	Adenoca. well	II	2yr. lost
6	75	F	Cholangitis	Infilt.	Fundus	2.6	Adenoca. mod	III	1yr. lost
7	74	M	Cholecystitis	Nod.-Infilt.	Body	5.0	Adenoca. well	III	1yr. lost
8	75	F	GB empyema	Infilt.	Entire	8.5	Adenoca. mod	III	5mo. died
9	82	F	Peritonitis	Infilt.	Entire	8.5	Adenoca. well	V	1wk. died
10	52	F	Peritonitis	Infilt.	Neck	1.8	Adenoca. well	V	5mo. died

* Infilt.: Infiltrative type, Nod.-Infilt.: Nodular infiltrative

** maximal diameter of carcinomatous lesion or the sum of the diameters in the cases with multiple lesions

DISCUSSION

In the present study, the incidence of GB carcinoma was 1.89% among GBs removed for benign biliary disease. It has been reported that 0.3-1.9% of patients who underwent cholecystectomy were found to have carcinomas in the GB (7, 9, 10). Bergdahl (9) reported that the incidence of GB carcinoma diagnosed first at pathologic examination was 0.3% of the cholecystectomized GBs for benign diseases. Kimura et al. (14) reported that the 0.5% of the incidence of asymptomatic GB carcinoma in autopsy cases. They examined GBs with serial sections at 5-mm interval as in our method. The incidence of GB carcinoma varies according to the characteristics of subjects; age, sex, incidence of cholelithiasis. The incidence of unsuspected GB carcinoma in this study is somewhat high, though it could not be compared with those in other studies because of difference in patients selection. One possible explanation is that preoperative investigation by ultrasound alone was insufficient for the detection of GB carcinoma. On the other hand, it may have been possible for us to detect microscopic carcinomas because the resected specimens were entirely examined using the stepwise tissue section method with mapping.

Early diagnosis of GB carcinoma is difficult because of its nonspecific symptoms and signs. The clinical manifestations of GB carcinoma are usually identical to those of cholecystitis and cholelithiasis and occur insidiously with the advancing of the stage (4, 7). The association of cholelithiasis with GB carcinomas has been well documented (15). The incidence of gallstones in patients with GB carcinomas ranges from 60% to 92% (4, 7, 9, 16). In this study, 90% of the patients with unsuspected GB carcinoma had gallstones. It was suggested that longstanding chronic inflammation by cholelithiasis plays a role in carcinogenesis.

Despite marked advances in biliary tract imaging, diagnostic accuracy is not satisfactory in cases with GB carcinomas. Abdominal US is a valuable screening imaging modality for carcinoma of the biliary tract. GB carcinoma can be recognized by polypoid mass or focal thickening of the GB wall (17). However, the diagnostic accuracy for abdominal US is still limited and US can detect only 30-50% of GB carcinomas (6-8, 18). Abdominal CT showed a diffuse or focal GB wall thickening and contrast enhancement of the GB wall. Bile duct obstruction, lymphadenopathy or direct liver invasion are often detected in conjunction with a GB mass (19). Recently, endoscopic ultrasound (EUS) has been shown to be a valuable method for the detection and staging of GB carcinoma (18, 20).

The operative management for GB carcinoma is de-

pendent upon the stage of disease. Curative surgery is possible only for 10-30% of the patients who undergo the operation (4, 5, 7, 21). In this study, simple cholecystectomy was performed in the patients with unsuspected carcinoma of the GB. The survival rate in the cases with early GB carcinoma was satisfactory. At present, simple cholecystectomy is considered an adequate therapy for early GB carcinoma, especially for the stage I disease (22). However, some authors recommend radical resection even for early GB carcinoma because lymph node metastases are common in the early stages (18, 23, 24). Radical operation should be carried out in the advanced stage of the disease to improve the prognosis of the patients (21). Recently, laparoscopic cholecystectomy has become a popular technique for the management of cholelithiasis.

There is a possibility of tumor implantation at the laparoscopic port sites in the case of unsuspected GB carcinoma during the operation (25). Therefore, it is important to establish early detection and accurate staging of GB carcinoma for the curative operation.

Preoperative diagnosis was difficult because a grossly infiltrative pattern was a common finding in our cases of unsuspected GB carcinoma. Particularly, dysplasia or carcinoma in situ of GB can not be distinguished from chronic cholecystitis grossly and can be easily overlooked on macroscopic examination (26). In this study, early carcinoma was discovered microscopically only within dysplastic mucosa in one case (case 2). It has been reported that preoperative or intraoperative diagnosis was more difficult in superficial type than in protruded type of early GB carcinoma (23, 27). Suspicious lesions in the GB should be examined microscopically at operation and thorough pathologic examination of the resected specimen is needed to identify the inapparent carcinoma of the GB.

Good prognosis is expected in the patients with GB carcinoma discovered as incidental findings (9, 11, 12). One reason for this is that many cases of unsuspected GB carcinoma belong to a relatively early stage of the disease. Early carcinoma of the GB may be defined as carcinoma confined to the mucosa or muscularis layer (24, 28). These early stages have a good prognosis after surgery and rarely show lymphatic or venous invasion (2, 18, 22, 28). But the nonspecific symptoms and signs of early GB carcinoma and the high percentage of superficial type make preoperative diagnosis very difficult (18, 23, 26).

In this study, about a half of the cases of unsuspected carcinoma were found to have early carcinoma and all of these cases diagnosed during that time were detected in the pathologic examination. There was no neurovascular invasion in these cases of early carcinoma and their

clinical outcomes were good. More recently, EUS and percutaneous transhepatic cholecystoscopy (PTCCS) have been shown to be valuable for the detection and confirmation of early GB carcinoma (18, 20). Unfortunately, they are expensive and not always available for use at present.

The present study indicates that the incidence of unsuspected GB carcinoma is not rare and a considerable number of the unsuspected cases are at an early stage of disease. Therefore, we should consider a possibility of presence of GB carcinoma in the evaluation of the benign biliary disease for a better prognosis.

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