High coincidence of Mirizzi syndrome and gallbladder carcinoma

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Background. *Mirizzi syndrome is a rare complication of long-standing cholelithiasis. It is defined as obstructive jaundice caused by external compression of the common hepatic duct by an impacted stone in the gallbladder neck. Gallstone disease and cholelithiasis-associated chronic biliary inflammation may play a causative role in the pathogenesis of gallbladder carcinoma. The purpose of this study was to investigate the coincidence of gallbladder carcinoma associated with Mirizzi syndrome. Furthermore, the diagnostic value of elevated CA 19-9 levels as indicator for a coincidental gallbladder carcinoma in this syndrome was studied.*

Methods. *Patient demographics, clinical findings, laboratory data, results of diagnostic studies, pathologic reports, and intraoperative findings of 1579 patients undergoing cholecystectomy were obtained from patient records and were retrospectively studied. Only patients with proven Mirizzi syndrome (i.e., extrinsic mechanical compression of the common hepatic duct by impacted gallstones, associated chronic cholecystitis, and a history of jaundice) were included in this study.*

Results. *Eighteen cases of Mirizzi syndrome (1.0%) out of 1759 cholecystectomies performed between January 1986 and March 1995 were identified. The seven male patients and 11 female patients had an average age of 74.8 years (range, 32 to 87 years). In five of these patients (27.8%) coincidental cases of gallbladder carcinoma were detected. The incidence of unsuspected malignancies in long-standing gallstone disease was 36 (2%) of 1759 and was statistically significantly different ($p < 0.001$) from the incidence in patients with Mirizzi syndrome (27.8%, 5 of 18). No significant difference was noted in age, gender, duration of jaundice, and type of lesions between these two groups. Tumor-associated antigen CA 19-9 level was elevated in 12 patients with Mirizzi syndrome, but it was significantly higher ($p < 0.0001$) in all five patients with coincidental gallbladder neoplasm and peaked at 1000 units/ml. All patients diagnosed with gallbladder carcinoma died within 18 months after operation.*

Conclusions. *There is high association of gallbladder cancer in Mirizzi syndrome. Elevated CA 19-9 levels in this syndrome are indicative of a coincidental gallbladder malignancy. Because of this high coincidence of Mirizzi syndrome and gallbladder cancer we recommend an intraoperative frozen section of the gallbladder in all patients presenting with Mirizzi syndrome. (Surgery 1997;121:58-63.)*

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MIRIZZI SYNDROME IS A RARE complication of long-standing gallstone disease that occurs in 0.7% to 1.4% of all cholecystectomies performed.[1-3] In 1948 Mirizzi[4] defined this syndrome as a common hepatic duct obstruction caused by an impacted stone in the gallbladder neck or cystic duct. In 1982 McSherry et al.[5] expanded the concept of Mirizzi syndrome into two types on the basis of the progression of the inflammatory process. They described a type I lesion as an extrinsic compression of the adjacent common hepatic duct and a type II lesion as a pressure necrosis of the septum between the cystic and common hepatic ducts leading to a cholecystocholedochal fistula.

Evidence exists of an association between long-standing gallstone disease and carcinoma of the gallbladder. The precise biologic mechanisms of this association are still unclear, and it remains an interesting and historically controversial subject.[6-8] More than 95% of reported cases of gallbladder carcinoma harbored coexistent gallstones. Chronic biliary inflammation has been found as the hypothetical link between gallstone disease and gallbladder cancer and relates to the chronic mechanical damage on the mucosa of the gallbladder.[9, 10] Kowalewski and Todd[10] were able to demonstrate in an

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Table I. Patients with Mirizzi syndrome listed by age, gender, type of lesion, symptoms, histologic findings, and laboratory data

Patient no.	*Age (yr)*	*Gender*	*Type of lesion*	*Symptoms*	*Histologic finding*	*Laboratory data*				
						WBC ($\times 10^3$)	*Total bilirubin (mmol/L)*	*GPT (units/L)*	*Alk P (units/L)*	*CA 19-9 (units/L)*
1	80	F	I	History of jaundice	Chronic cholecystitis	10.1	32	432	125	30
2	68	F	II	History of jaundice, RUQ pain	Chronic cholecystitis	14.3	24	150	61	14
3	79	M	I	Jaundice, pruritus	Shrunken gallbladder	6.2	75	453	342	112
4	82	M	II	Jaundice, fatigue, weight loss	Chronic cholecystitis	10.3	52	222	79	—
5	32	F	I	Jaundice	Chronic cholecystitis	8.2	49	125	118	43
6	79	F	II	Weight loss, jaundice, pruritis	Carcinoma pT2	13.4	178	313	126	1296
7	87	F	I	RUQ pain, fever, history of jaundice	Acute cholecystitis	17.9	16	125	59	132
8	78	M	I	Jaundice, RUQ pain	Acute cholecystitis	14.9	21	79	42	20
9	64	M	II	History of cholangitis, jaundice, pruritus	Chronic cholecystitis	13.7	125	318	119	362
10	66	F	II	Fever, pain, jaundice	Chronic cholecystitis	9.3	56	111	92	—
11	70	M	II	Jaundice, pruritus	Carcinoma pT3	11.2	364	157	490	1206
12	68	F	II	History of cholangitis, fever, jaundice	Chronic cholecystitis	18.9	159	81	123	512
13	86	F	II	Jaundice, weight loss	Carcinoma pTis	10.0	89	52	76	812
14	72	M	I	RUQ pain	Acute cholecystitis	14.6	23	46	29	—
15	82	F	II	Jaundice, pruritus	Chronic cholecystitis	11.0	212	110	256	189
16	85	F	II	Jaundice weight loss	Carcinoma pT1b	8.9	157	102	136	793
17	86	F	II	Jaundice, pruritus, fatigue	Carcinoma pT2	13.1	289	150	310	828
18	82	M	I	RUQ pain	Chronic cholecystitis	13.7	20	28	47	79

WBC, White blood cell count; *GPT*, glutamate-pyruvate transaminase; *Alk P*, alkaline phosphatase; *RUQ*, right upper quadrant.

Table II. Rate of developing neoplasms in gallstone diseases

n	*Coincidental gallbladder carcinomas*	*% of gallbladder carcinoma*	*Statistical significance (chi-squared test)*
Overall cholecystectomies, 1759	36	2.04	$p < 0.001$
Cholecystectomies for Mirizzi syndrome, 18	5	27.78	

experimental model that continuous damage of the gallbladder mucosa renders the epithelium susceptible to the effects of carcinogens. Tumor-supressor gene p53 and *ras* oncogenes have been described as biliary tract associated carcinogens playing a direct role in developing biliary neoplasms.[11] Biliary stasis is also another factor increasing the risk of gallbladder neoplasms.[12] In Mirizzi syndrome all those factors of carcinogenesis occur and lead to the hypothesis of a direct relationship to the development of gallbladder carcinoma. Since the original description of this rare syndrome, various reports of large series have been published,[13-15] but the association of chronic hepatic duct obstruction by an impacted gallstone and gallbladder carcinoma has been revealed in none of them.

In this study we report our findings of a highly significant coincidence of Mirizzi syndrome and gallbladder carcinoma, which has not been described in previous reports. This may provide support for the causative role of long-persisting cholecystitis by gallstones in formation of carcinoma of the gallbladder.

PATIENTS AND METHODS

In this study only patients with extrinsic mechanical compression of the common hepatic duct by impacted gallstones, associated chronic cholecystitis, and history

Fig. 1. Well-differentiated adenocarcinoma of the gallbladder, stage pT1b (patient 16). Superficial papillary layer of cylindric tumor cells in neck covered by inspissated mucus *(arrows)*. In other parts the tumor infiltrated the whole wall, which is densely fibrotic and moderately inflamed *(bottom)*. Hematoxylin-eosin stain; original magnification ×90.

of jaundice were included. Patient demographics, clinical findings, laboratory data, results of diagnostic studies, pathologic reports, and intraoperative findings were obtained from patient records. Follow-up was carried out at a mean of 48 ± 4 months after cholecystectomy and was obtained by personal follow-up or telephone inquiries. Preoperative diagnostic studies included abdominal ultrasonography as screening method and endoscopic retrograde cholangiography (ERC) for investigating the biliary tract diseases. Conventional cholecystectomy was performed 1 day after ERC under perioperative antibiotic treatment for 96 hours. All cholecystectomies were performed with open technique as described in a previous report.[2] Partial resection of the gallbladder for type I lesions and choledochoduodenostomy for type II lesions were the basic surgical concepts. Frozen section of the gallbladder wall was obtained during operation.

Statistics. Results are given as the mean ± SD in units. ANOVA and Student's *t* test and chi-squared test with Yates correction were applied to calculate for statistically significant differences.

RESULTS

Between June 1986 and March 1995, 18 patients (11 female and 7 male) with Mirizzi syndrome were admitted to our department and were treated surgically, representing 1% of 1759 cholecystectomies performed during this period (average age, 74.8 years; range, 32 to 87 years).

During this period 195 patients with gallbladder carcinoma were also observed, and 124 patients of this group were operated on, accounting for 7.05% of all cholecystectomies performed. The analysis of patients with gallbladder neoplasm without Mirizzi syndrome showed a mean age of 77.1 years (range, 51 to 92 years), with 62% of patients older than 70 years of age. No significant difference was noted in mean age between the patients with gallbladder cancer without Mirizzi syndrome and the group of patients with Mirizzi syndrome and coincidental gallbladder cancer. The history of preexistent gallstone disease in all patients with Mirizzi syndrome and a coincidental gallbladder malignancy was longer than 9 years (mean, 10.4 years; range, 5.2 to 16 years) and was considerably longer than in those patients with Mirizzi syndrome but without gallbladder cancer (mean duration, 6.8 years; range, 5.4 to 8.5 years).

The diagnosis of an existing Mirizzi syndrome could be confirmed with ERC examinations in all patients, but no coexisting carcinoma of the gallbladder was found before operation. During operation all our patients with Mirizzi syndrome had an induration and thickening of the gallbladder wall. Seven type I lesions and 11 type II lesions were found. A "porcelain" gallbladder was not observed. Obstruction or compression of the common hepatic duct producing the jaundice was caused exclusively by impacted gallstones in Hartmann's pouch or gallbladder neck. Chronic inflammation was not due to neoplastic involvement of the biliary tree, which could be confirmed by histologic examination in all cases. The clinical presentation of patients with Mirizzi syndrome varied according to the underlying severity of inflammation and type of lesion (Table I).

Seven of 18 patients underwent common bile duct exploration and had T-tube choledochostomy for 10 days. Prolonged compression of the common duct causing cholecystocholedochal fistulas required Roux-en-Y choledochojejunostomy in eight cases. Three other patients underwent choledochoduodenostomy. In five (27.8%) of 18 patients (four female and one male) a cancer of the gallbladder was detected by means of intraoperative frozen sections. This is a statistically high significant difference ($p < 0.001$) in comparison with the overall detection of unsuspected carcinomas in cholecystectomy specimens (2.04%) (Table II). On histologic examination all of them were moderately differentiated or well-differentiated adenocarcinomas growing locally in an infiltrative pattern. They were found in

Table III. Increased tumor-associated antigen CA 19-9 in patients with Mirizzi syndrome is indicative of coincidental gallbladder carcinoma

Mirizzi syndrome	*n*	*Preoperative CA 19-9 (units/L)*	*Statistical significance (ANOVA)*
Without carcinoma	10	147 ± 67	$p < 0.0001$
With carcinoma	5	987 ± 153	

combination with chronic inflammatory reactions of the gallbladder wall with mononuclear infiltrate, submucosal and subserosal fibrosis, and resorbtion of bile solids (Figs. 1 and 2). Three of them were classified as pathologic T2 (pT2) stage (UICC) or pT1b; one patient had pT3 stage adenocarcinoma infiltrating into the cystic duct and liver bed. Another patient exhibited a carcinoma in situ. Our actual frequency of finding an unexpected gallbladder carcinoma in patients undergoing cholecystectomies was 1.82% (32 of 1759).

Preoperative patient and laboratory data according to the type of lesion are shown in Table I. Twelve (66.7%) of 18 patients exhibited an increased level of the tumor-associated carbohydrate antigen CA 19-9 in preoperative blood tests. In patients with a coincidental gallbladder neoplasm (5 of 18) the CA 19-9 levels were elevated up to 1300 units/ml (mean, 987 ± 153 units/ml). The raising of the CA 19-9 values in patients with Mirizzi syndrome without a coincidental carcinoma was only moderate, but it also increased (mean, 147 ± 67 units/ml). The statistical difference among these two groups is highly significant with a p value < 0.0001 (Table III). No statistically significant differences were noted among gender, age, type of lesion, and duration of jaundice in development of gallbladder cancer in patients with Mirizzi syndrome. No perioperative deaths occurred. One patient had a postoperative biliary leak for 2 weeks without signs of peritonitis and was treated conservatively with endoscopic papillotomy and positioning of a nasobiliary drain. We found three patients with type II lesions who had undergone radical surgery including tangential resection of the bile duct in whom a benign stricture of the common hepatic duct had developed 5, 8, or 10 months after operation. They were treated by endoscopic biliary stenting with good results.

The follow-up examination showed that all patients diagnosed with a coincidental gallbladder carcinoma died within 18 months after operation.

DISCUSSION

Mirizzi syndrome is a rare complication of cholelithiasis caused by external compression of the common hepatic duct by an impacted gallstone in the gallbladder neck. Carcinoma of the gallbladder is equally rare, and the percentage of gallbladder malignancies detected only at postoperative histopathologic examination amounts to 4.8% to 26.7% of all carcinomas and 1.2% to 4% of cholecystectomy specimens.[1, 2] Therefore the risk for developing a cholecystic neoplasm is 0.1% in patients with cholecystolithiasis. Ekbom et al.[16] recently reported a significant decrease in the incidence of bile duct cancer 10 or more years after cholecystectomy and concluded that gallstones may play a causal role in the development of gallbladder cancer.

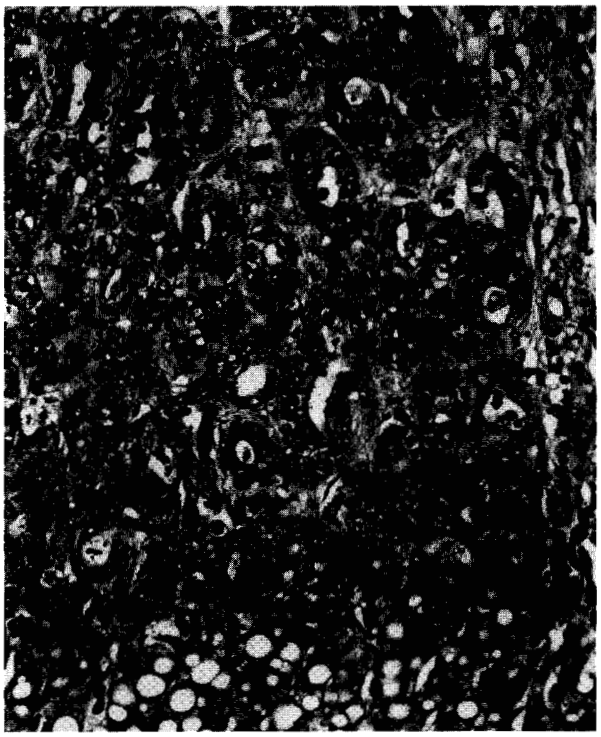

Fig. 2. Moderately well-differentiated adenocarcinoma of gallbladder, stage pT3 (patient 11). Tumor infiltrates broadly into liver bed. Liver tissue *(bottom)* shows fatty changes (steatosis). Hematoxylin-eosin stain; original magnification ×175.

Increased incidence of gallbladder cancer in the elderly, specificially in patients older than 70 years of age, has been shown in recent clinical studies. Thus the age of the patient may be an important factor in the development of gallbladder cancer. This hypothesis could also be supported with our data, but there was no link between the high coincidence of gallbladder cancer in Mirizzi syndrome regarding the mean age of our patients only. There have been few epidemiologic studies on gallbladder cancer, and most information on risk factors in gallbladder carcinogenesis stems from clinical series. The findings of formation of gallbladder cancer and its relation to cholelithiasis led to previous

reports by Polk[17] in 1966 and Broden and Bengtsson[7] in 1980 showing the association of long-persisting cholecystitis and gallbladder wall fibrosis. The most likely pathogenetic factor in biliary carcinogenesis is the presence of recurrent inflammatory processes within the gallblader superimposed by biliary stasis caused by the lack of sphincter function.[10, 12, 18, 19] In an experimental model in cats fecal clostridia were able to hydrogenate bile acids to carcinogens in a biliary stasis situation that secondarily caused cancer of the gallbladder.[9]

In Mirizzi syndrome all these factors are involved, especially the continous damage of the gallbladder mucosa by a mechanical alteration, and ulcerative cholecystitis may favor the conversion of bile acids to proliferative substances. In this report long-standing cholecystitis combined with ulceration and scarry deformation of the gallbladder wall presenting as type II of Mirizzi syndrome was found in all patients with coexisting gallbladder cancers, which stresses the hypothetical link between the factors of carcinogenesis in this disease. In recent years tumor-associated markers assumed an important role in the diagnosis and follow-up of pancreatic and biliary neoplasms. Since the first description of the carbohydrate antigen CA 19-9 as a nonspecific tumor antigen in 1979, it has been shown to be a sensitive marker for malignant pancreatic and biliary diseases.[20-23] Although mild elevations of CA 19-9 levels are seen in benign disorders of the biliary tract, markedly elevated levels greater than 1000 units/ml are reported in few benign processes only.[23] In our series of Mirizzi syndrome an elevation of CA 19-9 level has been reported in two thirds of patients, but it was significantly increased in all patients identified with a coexistent gallbladder carcinoma (Table III). The statistical difference between these two groups is highly significant. Therefore slightly elevated levels of CA 19-9 in the presence of Mirizzi syndrome can be explained by chronic inflammation of the bile duct or obstructive jaundice, but markedly elevated levels must lead to high suspicion of a coincidental carcinoma of the gallbladder. There are no signs or symptoms to distinguish patients with a coexisting carcinoma from those with Mirizzi syndrome alone, because most of the gallbladder carcinomas grow silently and mostly remain undetected during operation. A radical and aggressive approach is needed for potentially curative surgery but offers a chance only if the malignancy is detected at an early stage. Gallbladder carcinomas invading the muscle layer (pT1b) or even more advanced pT stages show a very poor outcome. Therefore the diagnosis of an unsuspected early tumor stage confined to the mucosa (pT1a) is very important and may lead to the best prognosis.[24, 25] If a pT1a or pT1b stage of the gallbladder carcinoma is found after operation, a second procedure for radical and extended tumor resection may offer a chance of longtime survival. In recent reports from Japan a radical tumor resection including liver segment IV and removal of all lymphatic vessels in the hepatic ligament and behind the head of the pancreas were reported with the best chances of survival.[26, 27] In our series of Mirizzi syndrome associated with carcinoma the pT stage unfortunately precluded extensive resections.

We therefore recommend an intraoperative frozen section of the gallbladder wall in presence of Mirizzi syndrome, especially in cases with markedly elevated values of CA 19-9, to secure the diagnosis and to prevent a second procedure. In some cases an early tumor stage may be found and a radical resectional surgical procedure may be done without delay.

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