

## Acute septic cholelithiasic cholecystitis and adenocarcinoma of the gallbladder ; an interesting association

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### Abstract

**Background and study aims :** Primary carcinoma of the gallbladder may present as acute lithiasic cholecystitis that leads to severe septic complications. The correlation between severe sepsis of the gallbladder and primary carcinoma is unclear. The goal of the present study is to examine the relation between severe septic complications of lithiasic cholecystitis and primary carcinoma of the gallbladder.

**Patients and methods :** A group of 72 patients (22 males, 50 females, age range : 45-99, mean age : 68.6 years), with severe septic cholelithiasic cholecystitis was treated with emergency surgery after failure of conservative treatment, and patients found with primary carcinoma of the gallbladder were registered. The resectability and operability of the tumor were studied, as well as tumor staging and overall patient survival.

**Results :** During urgent surgery for severe septic lithiasic cholecystitis, 12 patients (12/72, 16.6%) were found with gallbladder carcinoma. Patients with septic acute lithiasic cholecystitis and carcinoma had a higher mean age compared to those without carcinoma (74.8 vs. 67.4yrs). Eleven of 12 (91.6%) carcinomas were inoperable, despite resectability of 8 out of 12 (66.6%), and overall patient survival was limited to a few months after surgery.

**Conclusions :** Severe septic complications in elderly patients with a long-standing history of gallbladder stones may co-exist with primary carcinoma of the gallbladder. The percentage of a gallbladder carcinoma detected in septic patients reaches up to 16.6%. Even if these patients have a poor general health, surgical intervention is a solution when they appear with severe septic clinical symptoms caused by gallstones or carcinoma, in order to avoid lethal sepsis. The possibility of a carcinoma hidden in the gallbladder must be in mind during surgery. Imaging studies before surgery may detect the carcinoma; in most cases carcinomas are inoperable, although colectomy may be performed during surgery. (*Acta gastroenterol. belg.*, 2007, 70, 267-270).

**Key words :** gallbladder, carcinoma, complications, diagnosis, cholecystitis, prognosis, mortality.

### Introduction

Primary carcinoma of the gallbladder is a rare malignant tumor with clinical symptoms that usually appear late during the natural history of the neoplasm and convey a dismal prognosis (4). Occasionally, cancer of the gallbladder may present incidentally as early carcinoma with variable prognostic significance.

Early carcinoma of the gallbladder is an unsuspected condition, incidentally discovered during laparoscopic or open cholecystectomy. It represents the stage with the best chance for survival after surgery. Preoperative diagnosis is not possible and the histological examination requires careful sampling with multiple sections (9).

Occasionally, the histological report is insufficient and provides a false negative diagnosis, while the correct diagnosis is apparent several months later, when symptoms of peritoneal spreading and metastases of the tumor appear in the liver or umbilical port site (15).

Advanced or invasive carcinoma of the gallbladder represents a mortal condition in the majority of affected patients; it usually coexists with cholelithiasis and the possibility of an invasive carcinoma discovered incidentally due to cholelithiasis is not rare. The percentage of carcinomas found in gallbladders removed due to cholelithiasis, ranges between 0.7% and 2.85%, according to different published reports (2,12,14,18). This correlation seems to be stronger in patients with acute cholecystitis, primarily in elderly patients where the incidence of primary carcinoma is greater than 10% (1). In the present study the correlation between acute septic cholecystitis and gallbladder carcinoma is analyzed.

### Patients and methods

A group of 72 patients (22 males, 50 females, age range : 45-99, mean age 68.63 years), with acute lithiasic cholecystitis was treated surgically after failure of conservative treatment and the appearance of severe sepsis, according to the clinical presentation and laboratory findings of patients. Conservative treatment was primarily based on maintenance of fluid and electrolyte balance, cessation of feeding and intravenous antibiotic therapy. The mean time of conservative treatment before surgery was 9 days. Patients who had pathological findings from the bile duct or the pancreas were excluded from the study in order to exclude a pancreatic or middle bile duct carcinoma.

Sixty-one patients (84.7%) had empyema of the gallbladder, which was diagnosed preoperatively with laboratory findings, imaging studies, and was confirmed during surgery by the presence of pus in the gallbladder.

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In two patients (2.8%), acute cholecystitis was complicated with subhepatic abscess. Nine patients (12.5%) had necrosis of the gallbladder wall or perforation with bile peritonitis. Bacterial cultures of the gallbladder content were performed on 60 patients. Twelve patients (16.6%) had a history of diabetes mellitus. Clinical symptoms related to cholelithiasis in patients' histories were carefully registered. The tumor stage was estimated according to the TNM system, based on the depth of invasion, metastasis to the lymph nodes, and the existence of distal metastases: In stages Ia and Ib, there was invasion of the mucosa and submucosa, respectively. In stage II, there was invasion of muscular layer without invasion of serosa or the liver. In stage III, there was invasion of the serosa or liver no greater than 2 cm from the gallbladder wall, or invasion of the cystic duct, or spreading in regional lymph nodes. In stage IV, there was expansion greater than 2 cm into the liver or adjacent organs, such as the peripancreatic, upper mesenteric and paraaortic lymph nodes, or distal metastases. The type of surgical operation and overall survival were recorded.

According to the time of diagnosis of malignant disease, patients were divided in two groups: patients diagnosed during surgery via frozen section diagnosis and patients diagnosed after surgery via regular pathology examination and histological report. An age/sex-matched control group of 69 patients was used for comparison; these patients had acute lithiasic cholecystitis without severe sepsis and were treated by early cholecystectomy (i.e. within first two days after diagnosis of acute cholecystitis).

A group of 45 patients (62.5%) had additional moderate or severe diseases (e.g. cardiovascular diseases, obstructive pneumonopathy, diabetes mellitus etc.), which should be under control prior to surgery. A group of 65 patients (90.3%) had a known personal history of lithiasis of the gallbladder, noting symptoms related to cholelithiasis in the last 12 months prior to surgery.

All patients were studied preoperatively with ultrasound- and conventional or dynamic helical computed tomography. Eight of the 12 (66.6%) patients found with cancer had US and CT findings compatible for a gallbladder carcinoma.

## Results

Twelve patients were diagnosed with carcinoma of the gallbladder (16.6%, 4 males, 8 females, mean age 74.8yrs). In the control group, no carcinoma of the gallbladder was found. (Yates-corrected  $\chi^2 = 10.52039$ ,  $P = 0.0012$ , statistically significant difference). The mean age in 12 patients with septic cholecystitis and carcinoma was higher than in 60 patients with septic cholecystitis with no carcinoma (74.8 vs. 67.4 yrs, two sided  $p = 0.001$ , statistically significant difference, Mann-Whitney U test). Six patients were diagnosed during surgery (2 of stage III and 4 of stage IV), and a radical

surgical resection was possible in only two cases. In the group of 6 patients diagnosed after surgery (1 of stage II and 5 of stage III), 3 were subjected to additional surgery, after completion of the histological report, for more radical resections of the liver bed of gallbladder and regional lymph nodes. Of the remaining 3 patients in this group, additional surgery was not possible on 2 patients due to extremely bad general health, and the remaining patient of stage II, survives 5 years after surgery and chemotherapy, with no recurrence found during the follow-up.

Of the 7 stage III patients, one died due to sepsis 6 days after surgery and the remaining 6 had a mean overall survival rate of 7.8 months. The four stage IV patients had a mean survival rate of 4.8 months. Fifty of 60 patients (83.3%) had positive bacteriological cultures and the majority of microorganisms were identified as Gram-negative aerobic or anaerobic species.

## Discussion

Primary carcinoma of the gallbladder is one of the most aggressive malignant neoplasias of the digestive system, and therefore, the five-year survival rate is not more than 1-5% for stages III and IV (6). The persistence of gallstones in the gallbladder has long been considered an etiological factor for carcinoma, while in younger patients abnormalities of the choledocopancreatic joint seem to be strongly correlated to carcinoma of the gallbladder (17). An inflammatory process correlates to carcinoma of the gallbladder, but the exact pathogenetic mechanism remains quite obscure at the present time. Chronic inflammation appears to predispose to the development of epithelial dysplasia, then to carcinoma in situ and subsequently to invasive carcinoma (20).

The majority of tumors are diagnosed and reported at advanced stage. Additionally, the identification of early tumors presents a significant risk of spreading during surgery (15). The diagnosis of carcinoma is based on imaging techniques, clinical signs and symptoms, tumor markers and histological examination of specimens during or after surgery. Early diagnosis is difficult for the following reasons: imaging techniques are represented by ultrasonography, computerised tomography, ERCP and endoscopic ultrasonography and are used to indicate an intraluminal mass (type I), a focal or diffuse wall thickening (type II), or a mass that replaces the gallbladder (type III). Diagnosis based on these techniques is reported to be difficult when acute inflammation is present (10,11,16,21). Clinical diagnosis is often difficult or even impossible, because carcinoma and other malignant tumours of the gallbladder may present atypically as empyema, acute cholecystitis, postcholecystectomy benign biliary stricture, carcinoma of the pancreatic head, gastric outlet obstruction and liver abscess. Frequently, there are unusual variations: the presence of common bile duct stones, supraclavicular lymph node metastases, Mirizzi's syndrome, inguinal lymph node

metastases, or umbilical metastases (7,8). In addition, besides clinical and imaging difficulty in diagnosis, the histological difficulty should be added as mentioned previously in early carcinomas. In relation to the clinical observations in patients studied, the following data should be emphasized: i) The higher mean age in patients with septic cholecystitis and carcinoma indicates that suspicion of malignant disease should be kept in mind before and during surgery in elderly patients. The increased prevalence of gallstone with age, the gallstone as a well-known risk factor for cancer of gallbladder, and a mean age more than 70 years at diagnosis of cancer of gallbladder suggest the incidence of acute cholecystitis and cancer of gallbladder increases with age during the lifetime. In elderly patients with acute cholecystitis, the possibility of concomitant cancer in gallbladder should be considered. If examination of the gallbladder during surgery by frozen section biopsy yields a positive result for carcinoma, the surgeon is obliged to perform a more radical operation. ii) All patients in this study had acute cholecystitis, one of the most common complications of lithiasis of the gallbladder. Although the carcinoma located nearby the cystic duct may induce acute cholecystitis, the main cause of acute cholecystitis is the obstruction of cystic duct by stone. The evolution of inflammatory process, the relapse or remission of inflammation is influenced by the presence of additional diseases (e.g. diabetes mellitus and immunosuppressant conditions), the presence or not of microbial agents in the bile, the advanced age and the possibility of a gallstone obstructing the cystic duct, to retrograde into the gallbladder lumen restoring the flow of bile to the bile duct. All patients had rapid evolution of acute cholecystitis to sepsis according to clinicolaboratory findings and the main goal of the surgeon prior to surgery was to treat the sepsis and the lithiasis of the gallbladder, although in 8 patients a carcinoma was expected according to US and CT findings. Six cases with advanced carcinoma were diagnosed intraoperatively (6 of 12 patients, 50%) and 6 postoperatively via histological report (6 of 12 patients, 50%), and only 2 of 6 were suspected for carcinoma. Prior to completion of the histological report, cholecystectomy appeared to be the treatment of choice. A total cholecystectomy of the intact gallbladder, which keeps the septic content in isolation from adjacent organs of the abdomen, prevented the macroscopic diagnosis of malignancy, after surgery, macroscopic examination of the gallbladder wall and content, revealed gallstones, pus, necrotic and abnormal wall tissues, and macroscopic signs of inflammation. Such observations suggest that in addition to imaging, clinical and histological difficulty in diagnosis, that of macroscopic difficulty during surgery must be included. iii) Only severe septic complications of lithiasic cholecystitis had a high incidence of primary gallbladder carcinoma (12 of 72 patients, 16.6%). In the group control, no patient with primary carcinoma was found. Besides the presence of obstructive gallstone in the

cystic duct, which could retrograde into the gallbladder, the presence of carcinoma results in more stable stenosis and obstruction of the cystic duct. That leads to bile stasis and microbial suprainfection, as seen by the increased number of patients with infected bile. iv) Open cholecystectomy was used instead of laparoscopic access as recommended in elderly patients with acute cholecystitis (13). The resectability of malignant disease in patients diagnosed during surgery was low: an operation with therapeutic and radical consideration was possible in only two patients (2 of 6, 33.3%). In cancer patients diagnosed after surgery via histological report, the resectability of tumour was high (6 cholecystectomies of 6 patients with tumor stage II and III, 100%). The operability in cancer patients was low, with only one patient with tumor stage II surviving for 5 years. Cholecystectomy is known to be a radical operation during early stage carcinoma (5), but is the treatment of choice for complicated and septic lithiasic cholecystitis. Patients undergoing additional surgery after the histological report (i.e. resection of the adjacent liver parenchyma and lymph node resection) had a low overall survival rate. More radical techniques, such as hepatectomy and pancreatoduodenectomy, were not in use in local advanced disease as they have been proved to be unsatisfactory (5). Complementary chemotherapy was used only in one stage II patient, although alternative methods of treatment, such as chemotherapy or X-ray therapy remain without contribution (19). v) The majority of patients had a long history of cholelithiasis. Despite their advanced age and extremely bad health, if they had undergone surgery sooner, an earlier stage tumor may have been found.

In conclusion gallbladder carcinoma must be suspected in elderly patients with severe sepsis during the course of acute lithiasic cholecystitis, due to its increased incidence in this setting. When lithiasis of the gallbladder becomes symptomatic, it must be treated by surgery despite advanced patient age and after controlling the possible additional diseases. The majority of patients with carcinoma are diagnosed during advanced tumor stages when the malignant tumor is inoperable, and therefore, the chance of survival is small. There are many diagnostic difficulties that prevent the diagnosis of malignancy during its evolution prior to the stage when the neoplasm becomes inoperable. Septic cholecystitis seems to be a very common presentation of primary invasive carcinoma. Thus, elderly patients with septic complications of the gallbladder must be under continuous clinicolaboratory examination, and symptoms should not be readily attributed to inflammatory processes, despite all clinicolaboratory findings suggesting a septic lithiasic acute inflammation.

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