*Asian Journal of Case Reports in Surgery*

*7(1): 1-7, 2021; Article no.AJCRS.64309*

# Papillary Adenocarcinoma of the Gallbladder: A Case Report

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Authors ES, TAS and GJK helped in conceptualization, designed the study, literature searches, experimental analysis, data analysis and acquisition, performed statistical analysis, edited and reviewed the original draft of the manuscript. All authors read and approved the final manuscript.*

***Article Information***

Editor(s):
(1) Dr. Ashish Anand, GV Montgomery Veteran Affairs Medical Center, USA.
(2) Dr. Arun Singh, Rohilkhand Medical College & Hospital Bareilly, India.
Reviewers:
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(2) Antonio Serafín Valero Liñán, Universitario De Albacete. Unidad Hpb, Spain.
(3) Ioannis Lazaridis Clarunis, St. Clara Hospital and University, Switzerland.
Complete Peer review History: http://www.sdiarticle4.com/review-history/64309

***Case Study***

***Received 08 November 2020***
***Accepted 11 January 2021***
***Published 08 February 2021***

## ABSTRACT

Gallbladder carcinoma is a rare cancer often originally diagnosed as other benign gallbladder ailments. Early diagnosis is difficult due to lack of symptoms and half of all cases are only incidentally found during surgery. Unlike adenocarcinoma, the most common pathologic subtype of gallbladder cancer; papillary adenocarcinoma is found in only 3-5% of gallbladder cancer cases and has a tendency for exophytic growth and early manifestation of obstructive symptoms. We present a case of a female presenting with complaints and signs suggestive of choledocholithiasis. However, during surgery, a gallbladder tumor and empyema were discovered, with tumor invasion into the bile duct and the pancreas. The patient subsequently underwent open cholecystectomy and total resection of the gallbladder. Pathologic examination subsequently showed papillary adenocarcinoma subtype of gallbladder carcinoma.

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*Keywords: Papillary adenocarcinoma; cholelithiasis, cholecystectomy; gallbladder; gallbladder carcinoma.*

## 1. INTRODUCTION

Gallbladder carcinoma is a rare gastrointestinal malignancy, especially in the developed world. In the United States, the incidence is about 1 to 2.5 cases per 100,000. The rates are somewhat higher in Native Americans and Asians, with 6-8.1 cases per 100,000 in South Korea [1]. Cholelithiasis is a major risk factor for gallbladder cancers, with 75-90% cases presenting with one or more gallstone on resection [2-4]. Other risk factors are female sex, advanced age, smoking, obesity, diabetes, anatomical anomalies and congenital cysts, and primary sclerosing cholangitis [1,4,5]. Chronic infections with *Salmonella* and *Helicobacter* can also increase risk for gallbladder cancer [6].

While early stage carcinoma has a good prognosis, the disease usually develops insidiously and 90% of cases are unresectable after diagnosis, allowing for a dismal prognosis [1,2]. The vast majority of gallbladder carcinomas are only incidental findings upon exploration of cholelithiasis [3]. Unfortunately, due to the likely advanced stage at diagnosis, locoregional recurrence risk after surgery is high. Vague early symptoms delay early diagnosis and prompt treatment, rendering the overall outcome to be very poor.

Pain is the most common initial symptom. In later stages, patients can present with general anorexia, weight loss, and later, jaundice [7]. Advanced staging, nodal involvement and possible recurrence occurs in most diagnosed cases, and the anatomy of the gallbladder being adjacent to the liver without a serosal layer enables quick hepatic invasion and metastasis [8]. The average overall survival can be as low as 6 months after diagnosis in many cases [1].

A vast majority of gallbladder carcinomas are of the adenocarcinoma subtype, with other, rare subtypes being papillary, mucinous, squamous, and adenosquamous subtypes. Papillary adenocarcinoma, found in about 3-5% of gallbladder carcinomas, is thought to have better prognosis than other subtypes due to early manifestation of obstructive symptoms, which helps for early diagnosis [1,2]. Despite the general aggressiveness of gallbladder cancers, the papillary subtype tends to show exophytic growth instead of murally invasive growth and subsequently has a better remission rate, although the majority of cases are still unresectable on initial presentation.

This study presents a case of gallbladder cancer and empyema incidentally discovered during open cholecystectomy for suspected choledocholithiasis. The patient had no cancer-related complaints and all initial findings pointed towards a biliary gallstone. Pathologic examination of the resected specimen showed a rare papillary adenocarcinoma of the gallbladder, with invasion into the pancreas.

## 2. CASE REPORT

A 53-year-old female presented with abdominal colicky pain in the right upper quadrant for two days. The patient also complained of jaundice for about a week prior to admission. There was no fever, nausea, or anorexia. There is a history of weight loss, but it was not significant. Physical examination revealed right upper quadrant tenderness and a positive Murphy's sign. The patient's initial blood investigations revealed elevation in ALP (282 u/L) and Gamma-GT (107 u/L); otherwise, all other lab results were normal, including CA 19-9 (<3 U/ml).

Preliminary abdominal sonography revealed findings of intrahepatic and extrahepatic cholestasis, with hyperechoic lesions of approximately 2 cm x 2 cm in size in the common bile duct (CBD) which raised suspicion of choledocholithiasis. A whole abdominal computed tomography (CT) scan was then done, which revealed distended gallbladder with regular mucosa and an isodense lesion (33HU) and mild CBD dilatation. Intrahepatic biliary tracts dilatation was also seen, concluding the presence of suspected differential diagnosis of sludge or mass. There was no other abnormality noted in the liver or pancreas.

All these findings raised primary suspicion of cholelithiasis or mass. Modalities for magnetic resonance imaging (MRI) / magnetic resonance cholangiopancreaticography (MRCP) were unavailable in the resource-limited settingand the patient was taken to surgery for an open cholecystectomy. During the surgery, a large (4.6 x 6.5 x 0.5) cm papillary tumor was visualized within the body of the gallbladder and a radical cholecystectomy with bile duct resection was

performed.Non-contiguous additional papillary areas were also identified within the fundus and the neck. No gallstone was found within the gallbladder. Pancreaticoduodenectomy (Whipple's procedure) was also considered along with extended right hepatectomy, however the patient was considered unfit for the resection and instead a small section from the head of the pancreas was taken for biopsy. Periportal, choledochal, retropancreatic, common hepatic, paracoeliac lymphnodes were removed, and sent for histopathologicexamination.

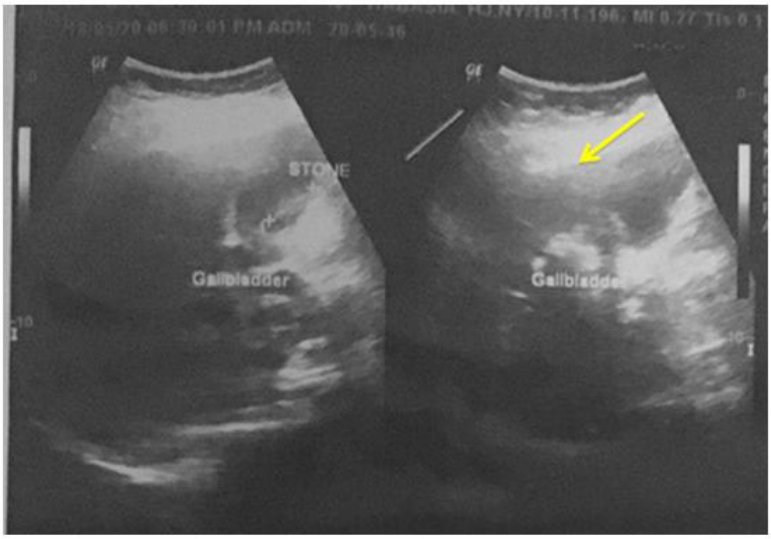


**Fig. 1. Ultrasonography (USG) findings of intrahepatic and extrahepatic cholestasis and hyperechoic lesions**

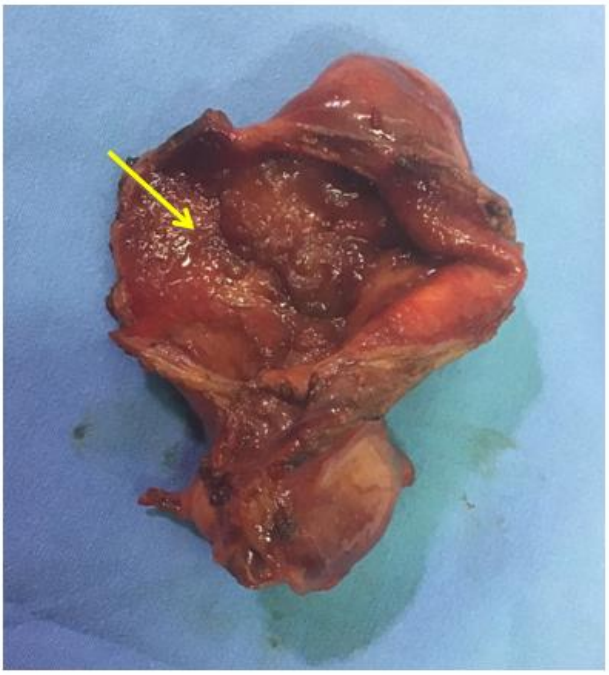

**Fig. 2. Gallbladder specimen**

The pathology revealed malignant glandular epithelial cells arranged in a papillary pattern, accompanied with increased vascularization and inflammatory cells infiltration. The pancreatic specimen showed the same finding, and a papillary adenocarcinoma of the gallbladder was concluded with the staging determined to be T3N1M0 (IIB). The patient's postoperative period was uneventful and she recovered well.Upon findings of malignant infiltration in the pancreas, the patient was offered a follow-up pancreaticoduodenectomy but the patient and family rejected further surgery and elected to undergo systemic chemotherapy. The patient proceeded to receive a chemotherapeutic regimen of 5-fluorouracil and gemcitabine; however, the regimen was administered in a different, more rural hospital due to travel restrictions caused by the coronavirus pandemic. A virtual multidisciplinary tumor board consisting of digestive surgeons and oncologists were called to determine this approach. The patient is still alive six months after initial surgery, although due to pandemic-related difficulties no further imaging and restaging were as yetperformed.

## 3. DISCUSSION

Gallbladder carcinoma is a very rare malignancy with poor prognosis. Like many other cancers, gallbladder carcinogenesis progresses with the metaplasia-dysplasia-carcinoma sequence, thought to progress over many years. Chronic gallbladder inflammation, such as by large gallstones or chronic infection, is a common risk factor, spurring cellular transformation and carcinogenesis [1,3]. Most gallbladder cancers show deep local invasion and high mortality, and most cases cannot be completely resected [2,9,10].0

A vast majority of cases, about 75 - 99% of gallbladder cancers, had a history of gallstones or a finding of stones intraoperatively [3]. The inverse, however, which is the incidental finding of gallbladder cancer during gallstone surgery, remains very rare. The presence of gallstones, and the chronic inflammation it causes, can spur carcinogenesis; larger stones are thought to increase risk and patients with stones larger than 3 cm are at 10 times more risk of patients with stones smaller than 1 cm [11]. Porcelain / calcified gallbladder also increases risk for gallbladder cancer. Polyps, bacterial infections, typhoid carrier, and congenital anatomic anomalies are also among identified risk factors [5,12]. Our patient has a unique situation where she presented with no history or finding of biliary stones, nor any other identifiable risk factors. Gallbladder cancer also show a predilection towards females- although the role of hormones in the pathogenesis has not been elucidated- as well as certain ethnic groups and geographical areas, such as Native Americans and Asians [1]. Only 2000-5000 cases are diagnosed each year in the United States, while the number in Korea is about three times that.

Adenocarcinoma is the most common subtype of gallbladder cancers, consisting of 80-97% of all gallbladder cancers, while the papillary, mucinous, squamous, and adenosquamous subtypes are much rarer. Papillary adenocarcinoma of the gallbladder, found in only 3-5% of cases, is unique amongst all the types as it has an unexpectedly good prognosis despite the generally aggressive nature of gallbladder cancers. This is thought to result from the subtype's predilection towards exophytic growth and its delayed intramural invasion [1,2].

Compared to the common subtypes, the papillary types of malignant neoplasms of the pancreatobiliary system seem to have a more indolent course, with slower progression from dysplasia to carcinoma [2]. Papillary carcinoma of the gallbladder have similar features with intraductal papillary mucinous cancers in the pancreas, as well as intraductal papillary neoplasms of the bile duct- thought to be the pancreatic and biliary tract equivalent of papillary gallbladder carcinoma; all these subtypes have exophytic tendencies and better prognosis than the common subtypes [1,7].

Delayed diagnosis of gallbladder cancer is common because symptoms early in the disease process are often vague, with the most common complaint being right upper quadrant pain around the hypochrondrium. The general presentation of gallbladder cancer can be divided into five groups [13]. Anorexia, weight loss, and generalized weakness are grouped into nonspecific symptoms that point towards malignancy. Biliary tract invasion can also cause jaundice, as this patient exhibited, and a poor prognostic factor as it indicates tumor invasion into the biliary tree [7]. This can be accompanied with nausea, vomiting, or pruritus in the advanced stages. Gallbladder cancer is also associated with Mirizzi syndrome [14]. Cholecystitis is also associated with gallbladder cancer, and either recurrent chronic cholecystitis without evidence of gallstone or acute

cholecystitis can accompany occult gallbladder neoplasms. This is most prominent in patients with elevated liver enzymes, and may also mask the initial diagnosis [15].

The papillary subtype differs in clinical presentation from the other subtypes as the exophytic growth can manifest obstructive symptoms at an early stage, and does not necessarily indicate profound tumor invasion like the common subtype. The early appearance of symptoms also facilitates in earlier presentation and diagnosis, although a vast majority of papillary gallbladder carcinoma still remain unresectable at the point of diagnosis [1,7]. Still, compared to the common subtype, the papillary subtype has a surprisingly high remission rate, especially if the tumor has not invaded the gallbladder wall.

Screening of all subtypes of gallbladder carcinoma remains a challenge, however, as laboratory tests are unreliable in diagnosing and identifying gallbladder carcinoma pre-operatively due to the low sensitivity. Both carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9) can be elevated in patients with gallbladder carcinoma, but both tests remain unreliable; the sensitivity of CEA is only about 50% and CA 19-9 is only 80% [16]. Our patient presented normal CA 19-9 levels, adding further evidence to the lack of reliability of tumor markers in predicting gallbladder cancer.

Advances in imaging have helped physicians in recognizing gallbladder cancer earlier, although about half of all gallbladder cancer is still only initially recognized during surgery. Ultrasonography remains the most common initial method and discontinuous gallbladder mucosa, mural thickening or calcification, mass, or direct liver infiltrations can indicate malignancy [17]. Dilatation of ducts, in the absence of gallstones, can also suggest obstructing malignancy. However, ultrasound can be more difficult in cases also involving primary sclerosing cholangitis. Endoscopic ultrasound may help define tumor depth and nodal involvement, and obtain biliary cytology through guided fine needle aspiration [18].

Computed tomography (CT) scans are inferior to USG in early detection, but can better assess resectability and disease extent. It is however poor in assessing omental spread and cholangiocarcinoma [19]. Endoscopic retrograde cholangiopancreatography can also be used to obtain biliary cytology, however it is now mostly replaced with noninvasive MRI/MRCP [20].

Complete surgical resection remains the only method to potentially cure gallbladder cancer, although data on the outcomes remain dismal due to the majority of cases presenting to surgeons in already advanced stages. A French survey concluded a median survival of 3 months and only 14% survival ratio at 1 year and 5% at 5 years [21]. Complete removal of the cancerous gallbladder and any adjacent organs, as well as all lymph nodes, and a clear histological margin is necessary to prevent recurrence; however, this is often unachievable in the surgical theatre. Positive prognostic factors include tumors still limited to subserosal mucosa; papillary or low-grade adenocarcinoma; lack of venous and neural invasion; and lymph node metastasis limited by the hepatoduodenal ligament [22].

Combination chemotherapy with gemcitabine and cisplatin show efficacy in increasing median survival of diagnosed patients [23]. Radiotherapy seems marginally useful, but often used as adjuvant therapy along with newer agents such as EGFR inhibitors [24].

## 4. CONCLUSION

Gallbladder carcinoma is a rare malignancy of the gastrointestinal tract. The presentation of gallbladder carcinoma may be very difficult to distinguish from benign pathologies like cholecystitis, and most cases often present at a later stage due to vague early symptoms and lack of sensitive screening modalities. Papillary adenocarcinoma of the gallbladder is a rare subtype of gallbladder carcinoma, with an exophytic growth pattern and predicted to have better prognosis. It may resemble cholelithiasis in imaging studies and present obstructive symptoms; however, due to its tendency to manifest symptoms at an earlier stage, this subtype has bigger possibility to be diagnosed early.

Our patient was a female aged 53 years, with complaints of dull pain and jaundice. Choledocholithiasis was suspected from the clinical presentation and preliminary imaging, however the tumor was confirmed during open cholecystectomy and histologic examination showed papillary type adenocarcinoma of the gallbladder. The case illustrates the challenge of early gallbladder carcinoma diagnosis, as well as the unique presentation of this rare subtype.

Early detection is crucial in reducing morbidity and mortality, as the rate of cure is significantly increased if the case is still completely resectable. Ultrasound findings of gallstones or polyps should be taken with additional consideration, and differential diagnosis of gallbladder carcinomas in patients with cholelithiasis symptoms can help in early discovery of tumor cases.

## CONSENT AND ETHICAL APPROVAL

Ethical approval was obtained through signed informed consent forms of the patient. Patient anonymity is ensured and no image or identification in this study can be used to identify the patient.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://www.sdiarticle4.com/review-history/64309*