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## Atypical presentation of an advanced obstructive biliary cancer without jaundice

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**Patient:** Female, 60  
**Final Diagnosis:** Cholangiocarcinoma  
**Symptoms:** Abdominal pain • abdominal discomfort  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Oncology

**Objective:** Unusual natural history/clinical course

**Background:** Cholangiocarcinoma remains to be a challenging case to diagnose and manage as it usually presents in advanced stage and survival rate remains dismal despite the medical breakthroughs. It is usually classified as intrahepatic, perihilar or distal tumor which can lead to bile duct obstruction causing sluggish flow of bile through the biliary tract and promoting increased absorption of bilirubin, bile acids and bile salts into systemic circulation accounting for the occurrence of jaundice, dark-colored urine and generalized pruritus. It usually becomes symptomatic when the tumor has significantly obstructed the biliary drainage causing painless jaundice and deranged liver function with cholestatic pattern. Jaundice occurs in 90% of the cases when the tumor has obstructed the biliary drainage system. A markedly dilated gallbladder as initial presenting feature in the absence of other typical obstructive clinical manifestations of an advanced stage of the cholangiocarcinoma is rare.

**Case Report:** This case report presents an atypical case of an elderly woman who presented with advanced metastatic ductal cholangiocarcinoma with markedly dilated gallbladder and liver mass without other clinical manifestations and laboratory evidence of cholestatic jaundice.

**Conclusions:** The mere presence of Courvoisier's sign, even in the absence of other signs of biliary obstruction, could be suggestive of advanced neoplastic process along the biliary tract. Laboratory evidence of cholestasis might lag behind the clinical severity of the biliary obstruction in cholangiocarcinoma.

**Key words:** cholangiocarcinoma • Courvoisier's sign • adenocarcinoma • obstructive jaundice

**Full-text PDF:** <http://www.amjcaserep.com/download/index/idArt/889620>

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## Background

Biliary tract cancer, which is traditionally divided into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater, is the second most common primary hepatobiliary cancer, after hepatocellular cancer. Clinical manifestation due to biliary obstruction tend to occur early if the tumor is located in the common hepatic duct, common bile duct or ampulla of Vater. The presence of distended gallbladder with dilated intrahepatic and extrahepatic ducts is typical seen in distal extrahepatic ductal cancers, cancers of the ampulla of Vater, intraductal gallstones or pancreatic cancer [1]. Despite the recent development of diagnostic and therapeutic approaches, this cancer remains a challenge to diagnose and treat with the 5-year survival rate considered generally poor. Patients would usually present at advanced stage of the disease and symptoms are non-specific like painless jaundice, weight loss or cholangitis [2].

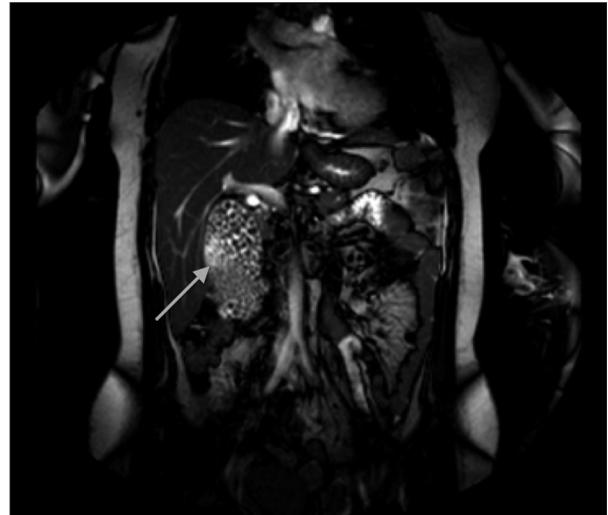
Arising from the epithelium of bile ducts either within the liver or along the biliary tract, cholangiocarcinoma can be categorized into 2 major clinical phenotypes: (1) intrahepatic mass-forming tumors (intrahepatic cholangiocarcinoma) and (2) large ductal tumors (ductal cholangiocarcinoma), both differing in etiology, risk factors, natural history, clinical behavior and response to therapy [2]. An increase in the frequency of intrahepatic cholangiocarcinoma has been reported in a cohort of cases over a period of 30 years in a single institution [3].

Though the pathogenesis is unclear, it was suggested that chronic biliary tract inflammation and cholestasis are associated with development of cholangiocarcinoma. Conditions identified as risk factors are primary sclerosing cholangitis, liver fluke, infection, hepatolithiasis, choledochal cysts, Thorotrast exposure, cirrhosis, Hepatitis C infection, toxins (polyvinyl chloride and dioxin) and biliary-enteric drainage procedures [4,5]. Variations in the incidence of the cancer in various races given the same environment have suggested the role of genetic influence in cancer pathogenesis. Just like other cancers, it is often associated with inactivation of tumor suppressor genes [5]. Genetic mutations in biliary transporter proteins have been linked in childhood onset of cholangiocarcinoma [6].

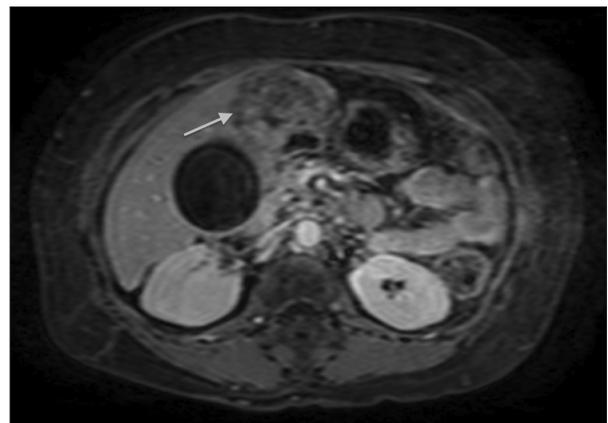
We present a case of an elderly female diagnosed with advanced ductal cholangiocarcinoma with liver metastasis presenting with Courvoisier's sign in the absence of cholestatic jaundice.

## Case Report

A 60-year-old female comes in with 3-day duration of worsening right upper quadrant and lower abdominal pain described



**Figure 1.** MRI (coronal view) of the abdomen showing the distended gallbladder (arrow) with multiple stones.

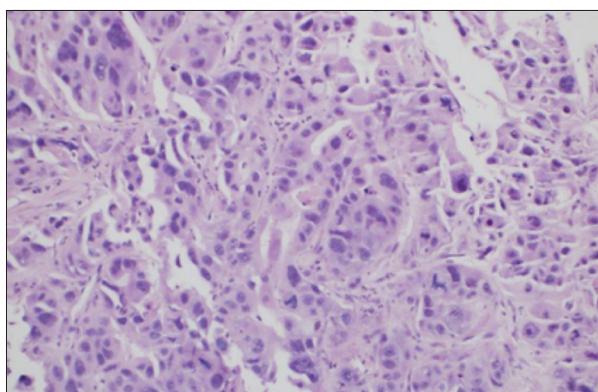


**Figure 2.** MRI (axial view) of the abdomen showing the left hepatic lobe mass (white arrow).

as sharp, constant, non-radiating without associated fever, chills, jaundice, weight loss, nausea, vomiting or changes in bowel movement. Her past medical comorbidities were hypertension, hyperlipidemia and osteoporosis. Physical exam revealed anicteric sclerae, soft abdomen with normal bowel sounds, palpable gallbladder and left lobe of the liver, no abdominal tenderness or guarding, no splenomegaly appreciated. Pelvic exam was remarkable for palpable right-sided pelvic mass. EGD was normal. Colonoscopy showed non-bleeding diverticulosis. MRI with contrast revealed a hypointense left hepatic lobe mass measuring 5.3 cm (craniocaudad) × 4.2 cm (AP) × 5.3 cm (transverse) with heterogenous and hyperintense T2 signal on T2 weighted sequences; an enlarged gallbladder (12.2×6×6.4 cm) with cholelithiasis without pericholecystic fluid (Figures 1 and 2). MRCP revealed intrahepatic biliary ductal dilation measuring approximately 1 cm with abrupt short segment narrowing in the extrahepatic common bile duct measuring 0.2 cm in diameter (Figure 3). The distal common bile duct

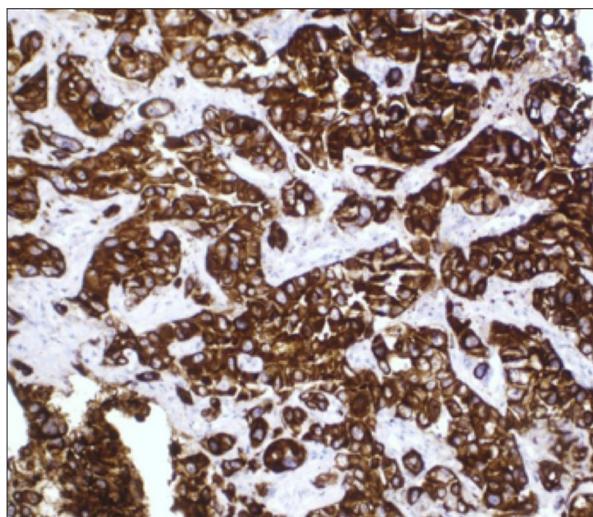


**Figure 3.** MRCP of the biliary tree showing the narrowing on the mid common bile duct (arrow).



**Figure 4.** Needle biopsy of the liver tumor showing high-grade carcinoma (H&E,  $\times 200$ ).

measures normal in diameter. There was no obvious filling defect to suggest choledocholithiasis. Initial hepatic function panel was deranged showing combined mild cholestatic pattern without bilirubinemia [Alkaline phosphatase: 89 U/L (30–115 U/L), AST: 32 U/L (5–40 U/L), ALT: 30 U/L (5–50 U/L), GGT: 91 U/L (3–40 U/L), LDH: 262 U/L (90–225 U/L), albumin: 3.5 g/dL (3.5–5 g/dL), total bilirubin: 0.52 mg/dL (0–1.5 mg/dL), bilirubin conjugated: 0.13 mg/dL (0–0.3 mg/dL)]. Tumor markers were significant for markedly elevated CA19-9 (12394 U/mL) with moderate elevation in CEA (394 ng/mL) and CA-125 (85 U/mL) while alpha fetoprotein tumor marker was within normal limits (3.89 ng/mL). Hepatitis A, B and C panels were nonreactive. ANA was negative while anti-mitochondrial antibody and anti-smooth muscle antibody were both positive at low titers, 1:20 and 1:40, respectively. Her coagulation profile was also within normal limits [PTT: 30 seconds (26–34 seconds), PT:

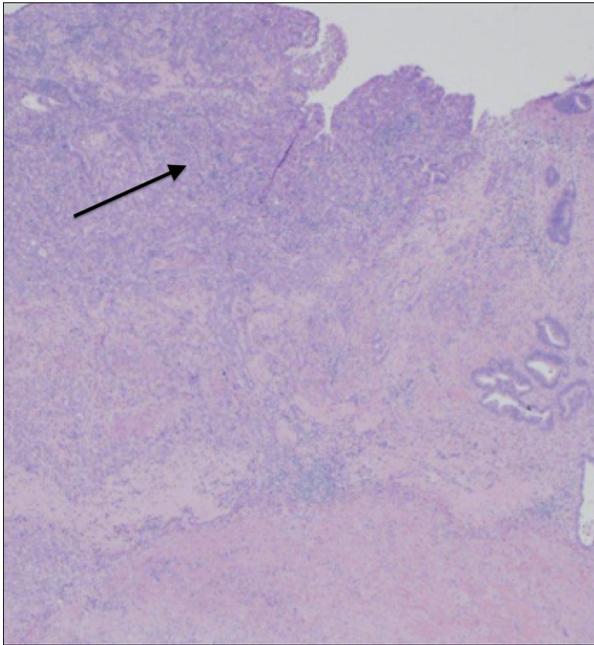


**Figure 5.** Needle biopsy of the liver tumor stained with cytokeratin CK 7 ( $\times 200$ ).

11.7 seconds (10–12.5 seconds) and INR 1.03]. CT-guided liver biopsy was obtained and histopathological exam revealed high-grade carcinoma (Figure 4). Epithelial nature was confirmed by positive stains for cytokeratins (Figure 5). Patient was then referred to Surgical Oncology Service.

A week before the surgery, patient developed jaundice with marked derangement in hepatic enzymes showing combined cholestatic and hepatitic pattern with conjugated bilirubinemia [Alkaline phosphatase: 363 U/L (30–115 U/L), AST: 174 U/L (5–40 U/L), ALT: 238 U/L (5–50 U/L), GGT: 493 U/L (3–40 U/L), LDH: 396 U/L (90–225 U/L), albumin: 4.2 g/dL (3.5–5 g/dL), total bilirubin: 12.1 mg/dL (0–1.5 mg/dL) and bilirubin conjugated: 7.3 mg/dL (0–0.3 mg/dL)]. Patient subsequently underwent surgical resection of the liver mass, cholecystectomy, and common bile duct resection with choledochojejunostomy. Intraoperative findings included a large gallbladder and a palpable mass within the mid-common bile duct acting as the source of obstruction for the gallbladder. There were no stones identified in the common bile duct. Histopathological examination revealed chronic cholecystitis with cholelithiasis, invasive poorly differentiated adenocarcinoma involving common bile duct, cystic duct and gallbladder neck (Figure 6). Liver mass, bile duct and portal duct resection margins were positive for carcinoma. Metastases were identified in the portal lymph nodes (Figure 7). Lymphovascular and perineural invasion were present.

Repeat serum CA 19-9 done a month after the surgery declined to 663 U/mL. Patient was then referred to Medical Oncology service which recommended combination of radiation treatment and chemotherapy (capecitabine). Prior to start of the radiation therapy, new hepatic lesions not within the radiation field were detected on CT scan of the abdomen showing



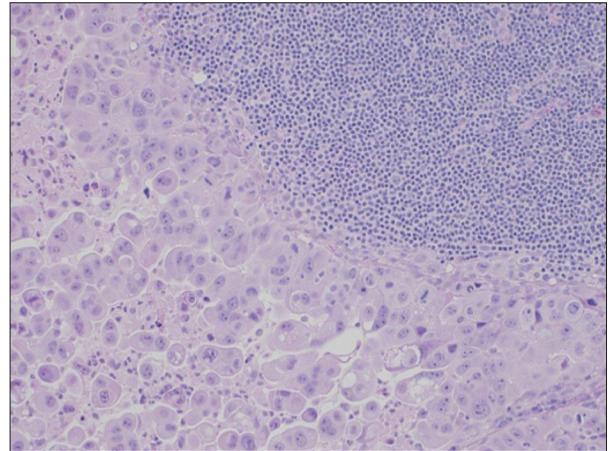
**Figure 6.** Poorly differentiated bile duct carcinoma (arrow) invading through the bile duct wall (H&E, ×40).

a 2.5 cm decreased attenuation at the anterior aspect of the right hepatic lobe with matted para-aortic nodes approximately measuring 2 cm. Meanwhile, the serum CA 19-9 increased to 3342 U/mL. It was decided to start patient on palliative chemotherapy regimen only without radiation treatment. Patient completed 3 cycles of gemcitabine plus oxaliplatin; however, progression of the disease was noted. Serial monitoring of serum CA 19-9 revealed progressively increasing trend, reaching as high as 13000 U/mL after 3 cycles of chemotherapy. Repeat CT scan of the abdomen and pelvis revealed interval increase in the size of the low density right hepatic lesion measuring 4 cm and increased in size of lymphadenopathy with findings suggestive of metastatic invasion of abdominal muscles and subcutaneous tissues. Due to progression of disease and worsening hepatic function, palliative chemotherapy was discontinued and patient decided for home hospice.

## Discussion

It has been reported that the major symptoms of cholangiocarcinoma were abdominal pain, weight loss, pruritus and jaundice but about one quarter of the patients were not clinically icteric. A palpable gallbladder (Courvoisier's sign) occurs rarely with cholangiocarcinoma, unless it arises from common bile duct distal to cystic duct. Most cholangiocarcinomas lie in the proximal upper third region [7].

Chronically increased ductal pressure is the probable cause of dilated gallbladders seen in malignant obstruction of the



**Figure 7.** Metastasis of the tumor in a lymph node. Tumor is shown in the left part invading the lymph node (H&E, ×200).

common duct. Patients with Courvoisier gallbladder usually have longer history of and deeper jaundice in presentation [8]. Gallbladder dilatation is usually associated with obstructive neoplastic process in the biliary tract but it could also manifest in benign common bile duct obstruction. The underlying mechanism suggested for the occurrence of Courvoisier's sign lies in structural changes in the gallbladder. Chronically elevated intraductal pressure from progressive malignant obstruction of the biliary tract is more likely to cause pressure-induced dilatation of the gallbladder while the presence of common bile duct stones could lead to intermittent episodes of cholecystitis leading to fibrosis of gallbladder, making it less likely to expand [9,10]. This clinical sign has been validated in a 2-year prospective cohort study which suggested that the gallbladder volumes measured by MRCP were significantly increased in patients with biliary tract obstruction secondary to neoplasm or stricture compared to the ones caused by choledocholithiasis [11]. In this case report, the presenting manifestations were suggestive of intrahepatic cholangiocarcinoma however the culprit lesion causing the dilated gallbladder was found to be the obstructing tumor at the common bile duct instead of the multiple gallstones within the chronically inflamed gallbladder (chronic cholecystitis). There were no intraoperative findings of the gallstones being found in the biliary drainage system. It has been recognized that the clinical phenotype of ductal cholangiocarcinoma encompasses cancers arising from within the large ducts at the hilum despite the presence of mass lesions or extensions into the liver [2].

Ductal cholangiocarcinomas which include cancers of common hepatic and common bile ducts characteristically present with signs and symptoms of biliary obstruction such as jaundice with laboratory findings suggestive of cholestasis while intrahepatic cholangiocarcinoma manifests typically with incidental liver mass lesion [2]. Our case was atypical in presentation

since patient already had distended gallbladder (Courvoisier' sign) suggestive of severe obstruction secondary to advanced biliary cancer despite the absence of clinical evidence of jaundice and laboratory evidence of bilirubinemia on initial presentation. Even though multiple stones were detected in the gallbladder, there were no stones identified along the common hepatic duct. The main focal point of obstruction was identified at mid-common bile duct due to the tumor. Furthermore, even though patient had ductal cholangiocarcinoma, liver mass was already evident both clinically and radiographically on presentation in the absence of typical clinical findings of obstructive biliary system like icterus, pruritus or dark-colored urine. La Greca et al. reported a similar case involving squamous cell carcinoma of the common bile duct presenting atypically without jaundice despite the proximal bile duct dilatation [12].

It has been shown in retrospective epidemiologic review that adenocarcinoma was the most common histologic type of biliary cancer which has an overall 5-year survival rate of 12.7% [13]. Frequent sites of metastases are liver and abdominal lymph nodes which were seen in this case [14]. Poor prognostic factors include mass-forming or periductal infiltrating macroscopic tumor type, lymph node metastases and vascular invasion [15]. Mortality is mostly attributed to biliary sepsis, liver failure or hemorrhage [2].

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## Conclusions

We presented a case of an elderly female with advanced biliary carcinoma with severe obstruction in the biliary tree causing Courvoisier's phenomenon but had remained anicteric and without bilirubinemia on initial presentation. This scenario may suggest that laboratory evidence of cholestasis might lag behind the clinical severity of the biliary obstruction in cholangiocarcinoma. The presence of Courvoisier's sign suggestive of possible malignant obstruction of the biliary tract could occur in the absence of other clinical markers of cholestasis.

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## Statement

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