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A case of primary squamous cell carcinoma of the gallbladder with local invasion of the liver and peritoneum, and metastasis to the omentum

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ABSTRACT

Primary squamous cell carcinoma of the gallbladder is a rare entity that comprises approximately 1%-3% of all primary gallbladder cancers. We report the case of a 37-year-old woman who was diagnosed with a locally invasive squamous cell carcinoma of the gallbladder. Surgical pathology revealed a predominantly squamous cell carcinoma composition of the tumor with a few microscopic foci of adenocarcinoma (<1% of tumor). We discuss pertinent clinical features, risk factors, and imaging characteristics to prompt early diagnosis and treatment, which will ultimately lead to improved patient outcomes.

Introduction

Gallbladder cancer (GBC) is the fifth most common gastrointestinal tract malignancy in the United States, with an incidence of 6500 cases annually [1]. Known risk factors for GBC include chronic cholelithiasis, female gender (ratio approximately 3:1), porcelain gallbladder, adenomatous polyposis of the gallbladder (GB), carcinogens (eg, miners exposed to radon), *Salmonella typhi* infection, and abnormal pancreaticobiliary duct junction [1]. Although only up to 3% of patients with cholelithiasis develop gallbladder cancer, gallstones are present in 70%-90% of patients diagnosed with GBC [1]. Chronic irritation of the GB wall related to gallstones is hypothesized to be the major risk factor for malignant transformation of the GB epithelium. Approximately 80%-95% of primary gallbladder cancers are adenocarcinoma (AC) [2]. Other histologic types include small cell cancer, squamous cell carcinoma (SCC), lymphoma, and sarcoma.

Patients with GBC are usually asymptomatic in the absence of advanced disease. As a result, diagnosis and management can be challenging. Patients can often present with symptoms such as anorexia, abdominal pain, nausea, and vomiting,

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which may be indistinguishable from those of acute cholecystitis [3]. Findings that are more specific for advanced disease include weight loss, obstructive jaundice (secondary to tumor invasion of the intrahepatic bile ducts or hepatic metastases), ascites, palpable abdominal mass, and hepatomegaly. Computed tomography and ultrasonography results are often consistent with acute cholecystitis and cholelithiasis. Thus, most cases are diagnosed intraoperatively.

Case report

A 37-year-old previously healthy Caucasian female presented initially with progressive right upper quadrant (RUQ) abdominal pain and pruritus. Her pain became increasingly worse 2 days prior to presentation. Review of systems revealed jaundice, scleral icterus, pruritus, fatigue, light-colored stools, and progressive abdominal distension, despite not having made any dietary modifications. She did not report weight loss, fever, chills, nausea, or vomiting. Social history reveals social alcohol consumption and a light tobacco smoking history. On examination, she was jaundiced, with a palpable RUQ mass. Her abdomen was soft and nontender. Laboratory findings demonstrated a WBC count of 7100/μL (normal: 3.8-10.5 K/μL), total bilirubin (T. Bili) of 7.3 mg/dL (Normal: 0.2-1.2 mg/dL), direct bilirubin (D. Bili) of 5.7 mg/dL (Normal: ≤0.2 mg/dL), alkaline phosphatase (Alk Phos) of >1000 U/L (Normal: 40-120 U/L), and Ca 19-9 of 45.0 U/mL (Normal: ≤41.3 U/mL). The initial computed tomography scan of the abdomen was interpreted to include intrahepatic biliary ductal dilatation, a dilated stone-filled GB up to 6.4 cm in diameter with an abnormally thickened wall up to 0.6 cm, and pericholecystic fluid, which was concerning for acute cholecystitis or choledocholithiasis. There was also an 8.4 cm heterogeneous soft tissue mass within the liver with an infiltrative component adjacent to the GB fossa (Figs. 1 and 2). A corresponding MRI demonstrated a focal defect in the

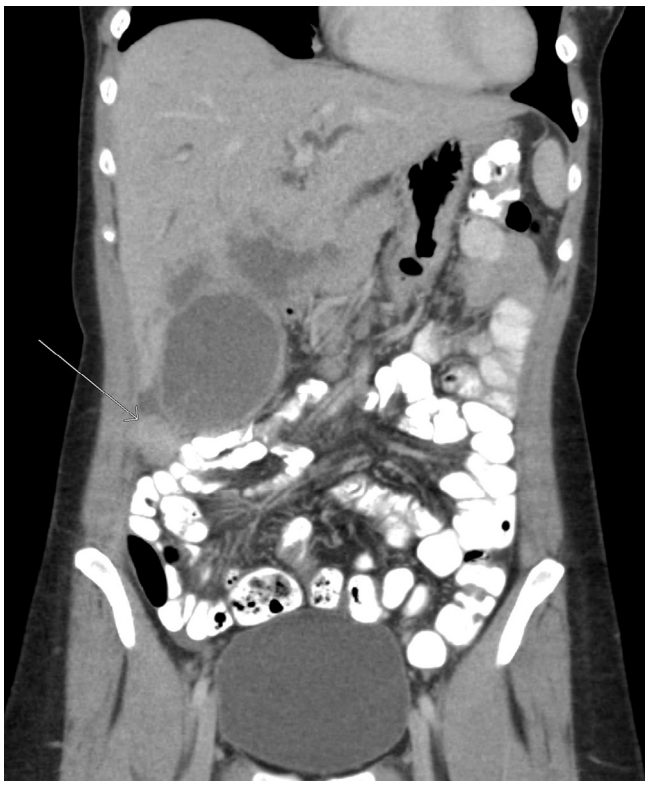

Fig. 1 – Coronal contrast-enhanced CT image of the abdomen demonstrates gallbladder wall thickening, pericholecystic hepatic lesions (tumor invasion), intrahepatic biliary ductal dilatation, as well as a soft tissue peritoneal lesion adjacent to the gallbladder (arrow). CT, computed tomography.

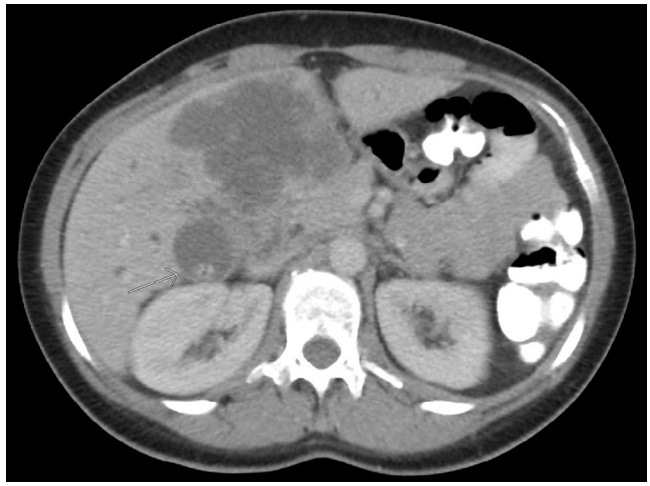

Fig. 2 – Axial contrast-enhanced CT image demonstrates large hypodense hepatic lesions, a distended gallbladder neck with stones (arrow), and intrahepatic biliary ductal dilatation. CT, computed tomography.

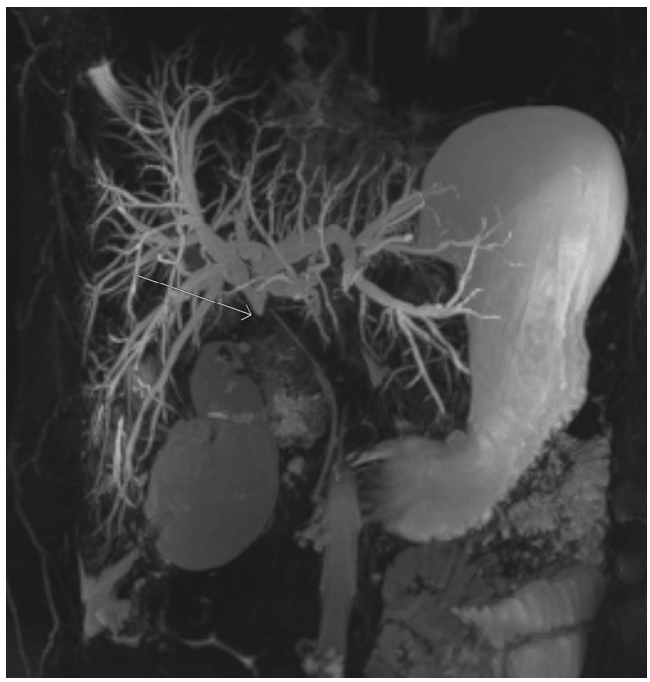

Fig. 3 – Coronal T2-weighted MIP image of the biliary tree demonstrating CHD obstruction (arrow). CHD, common hepatic duct; MIP, maximum intensity projection.

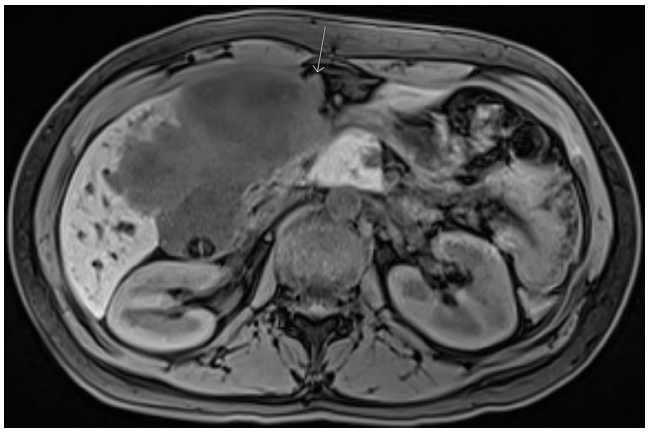

Fig. 4 – Axial T1-weighted precontrast image demonstrates heterogeneous, predominantly hypointense hepatic lesions, a peritoneal lesion (arrow), and cholelithiasis within the gallbladder.

anterior GB wall adjacent to the right hepatic lobe, likely related to GB wall necrosis in this region/acute gangrenous cholecystitis. Also noted was common hepatic duct (CHD) obstruction and a large 7.6-cm lesion in hepatic segment 4B, as well as a second smaller lesion within segment 5, which did not enhance with gadolinium (Figs. 3-5). As a result, a likely diagnosis of hepatic abscesses was given with consideration for a superimposed infiltrative neoplastic process.

Interventional radiology was consulted for placement of a cholecystostomy tube and drainage of hepatic abscesses. A cholecystostomy was placed with aspiration of approximately 150 cc of purulent bilious fluid. A large hypoechoic lesion in hepatic segment 4 was accessed and a drain was placed with aspiration of only a few cc of purulent fluid. Gram stain and culture of both specimens showed no growth of organisms.

Despite placement of a cholecystostomy tube and hepatic drain, T. bili remained elevated up to 7.9 mg/dL over the following 3 days. As a result, an ultrasound was obtained which redemonstrated a persistently dilated GB with an appropriately positioned cholecystostomy, a thickened GB wall, and multiple heterogeneous hepatic lesions, which were thought to be phlegmon or developing abscesses (Fig. 6). Gastroenterology (GI) was consulted and performed an endoscopic retrograde cholangiopancreatography (ERCP) with placement of a pancreatic duct stent as well as CHD stent placement for a visualized stricture. A CHD biliary brushing was performed at the time which was negative for malignant cells. Following the ERCP, her diet was advanced, her T. bili trended down to 3.3 mg/dL, and her WBC remained in normal range prior to discharge home.

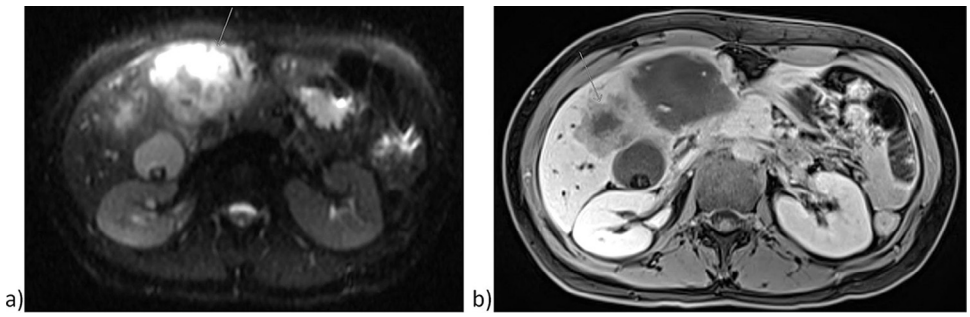

Fig. 5 – MRI: (A) Axial diffusion-weighted image demonstrates restricted diffusion within the periphery of one of the hepatic lesions (arrow). There is cholelithiasis within a distended gallbladder neck. (B) Axial T1-weighted contrast enhanced image (5-minute delay) demonstrates hepatic lesions with peripheral enhancement and central hypointensity (arrow).

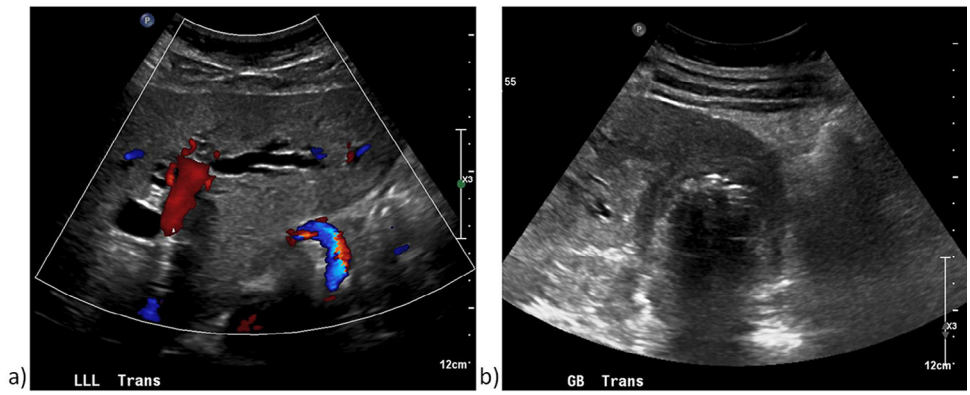

Fig. 6 – Ultrasound images: (A) Markedly dilated intrahepatic biliary ducts within the left hepatic lobe. (B) Marked gallbladder wall thickening, cholelithiasis, and adjacent hypoechogenic hepatic lesions or invasion.

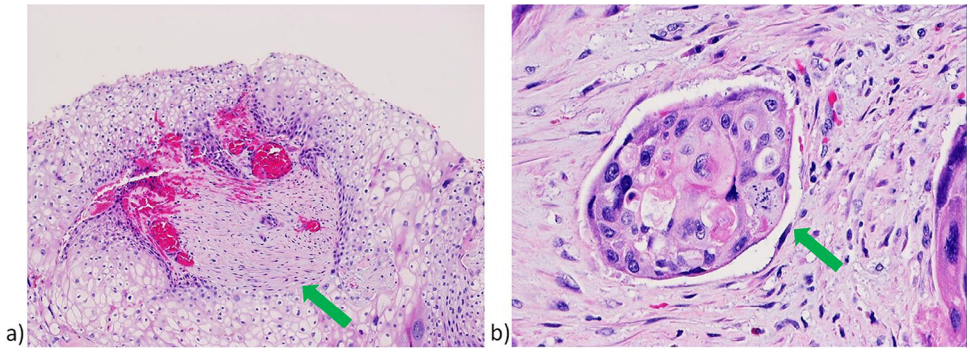

Fig. 7 – Microscopic pathology: (A) Nerve (green arrow) is surrounded and invaded by tumor nests (perineural invasion). (B) Lymphatic channel (green arrow) with tumor nest inside (lymphovascular invasion).

She presented again 1 month later with 1 day of severe RUQ abdominal pain. A repeat ERCP was performed with brushings of the CHD stricture which returned suspicious for SCC. The decision was made to perform a laparoscopic cholecystectomy. The previously seen peritoneal soft tissue mass adjacent to the GB was biopsied and sent for frozen section, which showed SCC. The gallbladder was resected. Histologic examination of the GB demonstrated stage T3NxM1 moderately differentiated invasive SCC with extensive necrosis involving the entire GB, as well as local invasion to the peritoneum and metastasis to the omentum (Figs. 7 and 8). A few microscopic foci of AC were also seen (<1% of total tumor volume). The patient was discharged to follow-up with another facility for further treatment.

Discussion

Primary SCC of the gallbladder is a rare entity that comprises between 1-3% of all primary GB cancers [4,5]. There is a poorer prognosis associated with primary SCC of the gallbladder when compared to the more common AC variant because it is thought to be more locally invasive, and is typically diagnosed at a more advanced T stage [2,4,6]. The overall mean survival rate for patients with GBC is 6 months, with a 5-year survival rate of 5% [3]. The gallbladder lacks a serosal layer between the gallbladder and liver, which increases susceptibility for local hepatic tumor invasion. This is why early diagnosis of primary SCC of the GB is critical for improved patient outcomes.

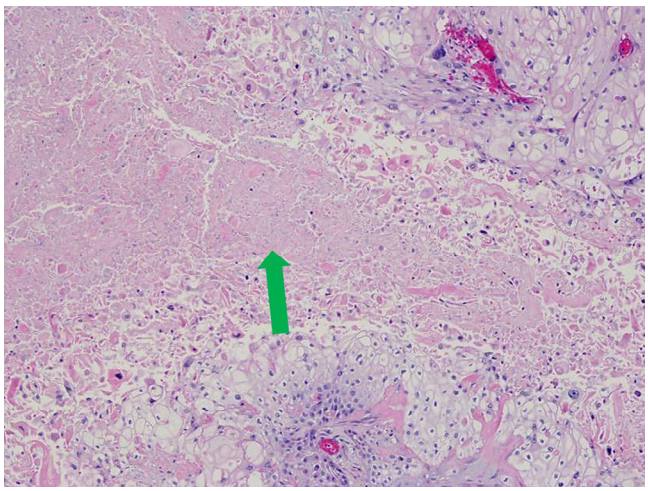

Fig. 8 – Extensive areas of tumor necrosis are identified (green arrow).

Song et al. demonstrate in their analysis of 411 patients with GBC, that there is no statistically significant difference of percentage of patients with normal or elevated Ca-19-9 levels. It cannot be reliably used as an indicator for disease, however, a larger number of patients with GBC had a CA-19-9 level >37 (U/mL) [2]. Song et al. also reported a median follow-up time of 21 months and demonstrated that patients with mixed adenosquamous carcinoma (ASC)/SCC differentiation had a median survival of 3.3 months compared to 6.0 months in the AC variant [2]. However, Kalayarasan et al. (136 patients) found no significant difference in survival rates between patients with SCC/ASC vs AC [6]. A summary of recently reported cases of SCC of the GB is presented (Table 1).

Radiographic features suspicious for gallbladder cancer include: intraluminal mass, diffuse mural thickening, mass replacing the gallbladder (present in 40-65% of cases at initial detection), intra-hepatic biliary ductal dilatation, and hepatic lesions adjacent to the gallbladder fossa [11]. More advanced features include peritoneal carcinomatosis, lymphadenopathy, and hepatic/distant metastases. Once we identify suspicious features, it is important to correlate with the history and imaging features for suspicious signs and symptoms, as well as risk factors.

The differential diagnosis for findings suspicious for gallbladder cancer include: gallbladder polyp, gallbladder wall thickening/edema (secondary to adenomyomatosis, portal hypertenion, hepatitis, infectious mononucleosis, congestive heart failure, renal failure, and pancreatitis), cholecystitis (including acute calculous, acalculous, chronic, and xanthogranulomatous variants), bile duct tumors, biliary obstruction, cholangiocarcinoma, hepatocellular carcinoma, gallbladder volvulus, and liver abscess.

As radiologists, it is important to keep GBC on the differential for patients with gallbladder wall thickening, intrahepatic biliary ductal dilatation, and/or adjacent hepatic lesions. It is also important to assess for regional lymphadenopathy. Although it has been described, regional lymphadenopathy is

Table 1 – Summary of recently reported cases of SCC of the gallbladder

Reference	No. of patients	Age	Gender	Presentation	Imaging findings/diagnostic modality (Dx)	Pathology	Involvement	Survival (mo)
Alpuerto et al. (2017) [4]	1	75	F	RUQ pain, WBC (15,000/μL), and Normal Liver Function Tests (LFTs)	CT: GB wall thickening, pericholecystic fluid, irregular soft tissue mass in GB fundus US: 3.8 cm Heterogeneous GB fundal lesion with small calcifications Dx: Cholecystectomy, duodenal/stomach resection	Pure 1° SCC of the GB T4NxMx	Local invasion of the liver, duodenum, and stomach	Alive at the time of publication
Chandna et al. (2016) [7]	1	70	F	Dyspepsia, RUQ pain, icterus, and no palpable mass	CT: Not performed US: Gallstones with a thickened irregular GB wall Dx: Cholecystectomy	Keratinizing SCC confined to the serosa	Locally resected tumor with negative margins	Not reported
Hoshimoto et al. (2016) [8]	3 SCC 1 ASC	Mean of 68	2:2 (M:F)	Not reported	Imaging findings were not reported	SCC (40%-90%) T2 and T3 stages	Local invasion of the liver	Not reported
Kalayarasan et al. (2013) [6]	4 (SCC) 10 (ASC[a])	Median of 49	1:2.5 (M:F)	Abdominal pain, emesis, and palpable RUQ mass	Imaging was performed but findings are not reported Dx: Staging laparoscopy and tumor resection	SCC/ASC stage T3 (43%) or T4 (57%)	Local invasion of the duodenum, CBD, liver, and colon	Median of 28
Khan et al. (2012) [9]	1	35	F	R-sided abdominal pain, palpable RUQ mass	CT/US: Enlarged GB up to 8.4 cm, thickened GB wall up to 0.8 cm, an 8-cm solid hepatic mass within the right hepatic lobe, and cholelithiasis Dx: Cholecystectomy and partial hepatectomy	Pure SCC stage T4N0Mx	Local invasion of the liver and omentum	Not reported
Mghirbi et al. (2016) [5]	1	67	F	RUQ pain, 15 kg weight loss, and palpable RUQ mass	CT: 8-cm solid cystic mass of the GB bed with intrinsic calcifications and extension into the adjacent liver parenchyma US: 10-cm heterogeneous GB mass with echogenic center and hepatic invasion Dx: Colonoscopic biopsy of a right colon lesion	SCC of the GB (R colon biopsy) T4NxMx	Local invasion of the liver and right colon	Not reported
Roa et al. (2011) [10]	8 (SCC) 26 (ASC[a])	Mean of 65	7:27 (M:F)	Specific presenting symptoms not included	Imaging was performed but findings are not reported Dx: Most cases following cholecystectomy for suspected acute cholecystitis	SCC/ASC stage T2, T3 (68%), and T4 at diagnosis	Local invasion of the duodenum, CBD, liver, stomach, and colon	ASC[a] mean of 23 Adeno mean of 50
Song et al. (2015) [2]	10 (SCC) 24 (ASC[a])	Mean of 61.4	10:24 (M:F)	Included abdominal pain, jaundice, weight loss, and palpable mass	Imaging was performed but findings are not reported Dx: Tumor resection	SCC/ASC stage T3 (38%) or T4 (62%)	88.2% with liver invasion	Median of 3.3
Levy et al. (2017) (this study)	1	37	F	Abdominal pain/distension, jaundice, pruritus, fatigue, pale stools, and palpable RUQ mass	CT: Intrahepatic biliary ductal dilatation, dilated GB with thickened wall, an 8-cm heterogeneous liver mass, and cholelithiasis US: Multiple heterogeneous hepatic lesions thought to be abscesses MRI: CHD biliary obstruction and 7.6-cm nonenhancing hepatic lesion	SCC (<1% adenocarcinoma) T3NxM1	Local invasion of the liver, peritoneum, and metastasis to the omentum	Alive at the time of publication

ASC, adenosquamous carcinoma; CBD, common bile duct; CHD, common hepatic duct; CT, computed tomography; Dx, diagnosis; GB, gallbladder; RUQ, right upper quadrant; SCC, squamous cell carcinoma; US, ultrasound; WBC, white blood cell.
ASC, adenosquamous differentiation (composed of cases with adenocarcinoma with more than 30%[a] or 25%[b,c] of the SCC component).

seldom reactive secondary to acute cholecystitis. However, there may be a rare instance where lymphadenopathy is present secondary to a superimposed infection such as infectious mononucleosis or a systemic lymphoproliferative disorder [12]. Albeit the SCC variant does not typically demonstrate local lymph node involvement, the more common AC variant does, and the presence of lymphadenopathy should increase suspicion for malignancy. The patient's risk factors should also be assessed to determine likelihood for GB cancer. Our patient's known risk factors are chronic cholelithiasis and female gender. Care should also be made to obtain as much history as possible because the provided history is often meager. The synthesis of both imaging features and clinical history should lead you to suspect GBC.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.radcr.2017.09.026.

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