

Adenocarcinoma of the Gallbladder: Incidental Finding in Patients following Laparoscopic Sleeve Gastrectomy and Cholecystectomy

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ABSTRACT: **Background:** Gallbladder (GB) cancer is rare. Most cases are incidentally found in specimens after a cholecystectomy. Cholelithiasis is almost always present when this diagnosis is made. Obesity is a known risk factor for gallstone formation and thus may be related to GB cancer.

Objectives: To highlight the importance of evaluating the gallbladder before surgery, resecting the gallbladder whenever required, and screening the resected tissue for malignancy.

Methods: We retrospectively searched a prospectively maintained database of all bariatric procedures during the last 8 years for cases of concomitant laparoscopic sleeve gastrectomy (LSG) and laparoscopic cholecystectomy (LC). Pathologic reports of the gallbladders were reviewed. Demographic data and perioperative parameters were documented.

Results: Of 2708 patients reviewed, 1721 (63.55%) were females and 987 (36.45%) males. Excluded were 145 (5.35%) who had a previous cholecystectomy. Of the remaining 2563, 180 (7.02%) had symptomatic gallbladder disease and underwent LSG with LC. Of these, two females (BMI 53 kg/m² and 47 kg/m², both age 60) were found by histological examination to have adenocarcinoma in their GB specimens (1.11%). Both were reoperated, which included partial hepatectomy of the GB bed, resection of the cystic stump, lymph node dissection, and resection of the port sites. One patient is doing well, with no evidence of disease at a postoperative follow-up of 4 years. The second patient had recurrent disease with peritoneal spread and ascites 20 months post-surgery and died 18 months later.

Conclusions: GB cancer is a rare finding in cholecystectomy specimens. The incidence of this entity might be higher in obese older females owing to the higher incidence of cholelithiasis in these patients.

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KEY WORDS: obesity, gallbladder cancer, bariatric surgery, laparoscopic sleeve gastrectomy (LSG), laparoscopic cholecystectomy (LC)

Obesity is a chronic disease and is associated with an increased risk of metabolic comorbidities and cancer [1]. Due to the increasing prevalence of obesity worldwide, it is important to clarify the impact of excess body weight on cancer and to elucidate the mechanisms involved. Morbid obesity with concomitant cholelithiasis is not uncommon. Gallbladder (GB) cancer in obese patients has not been fully characterized [2]. Obesity is a significant risk factor for GB stones and thus may be a risk factor for GB cancer.

We report here two cases of incidental GB cancer found at laparoscopic cholecystectomy (LC) performed during laparoscopic sleeve gastrectomy (LSG) for morbid obesity in elderly female patients.

PATIENT DESCRIPTIONS

We conducted a retrospective review of the 2708 cases that underwent weight loss surgery (WLS) during the last 8 years in a single institution. Excluded were 145 (5.35%) who had a previous cholecystectomy. Of the remaining 2563, 180 (7.02%) had symptomatic gallbladder disease and underwent bariatric surgery (BS) with LC. Of these, two cases of GB cancer (1.11%) were identified and analyzed. No intraoperative mishaps were identified in both cases. The diagnosis was made by histological examinations.

PATIENT 1

A 60 year old obese female patient with body mass index (BMI) of 53 underwent LSG with LC. No abnormalities were detected in her physical examination. The preoperative ultrasound confirmed the diagnosis of a 3.5 cm GB stone with associated GB wall calcification ('porcelain' GB). Routine laboratory testing (complete blood count and serum chemistry panel) did not reveal any abnormalities.

At laparoscopy, no obvious inflammation of the GB was observed and LSG with LC was performed. Inspection of the GB and liver showed no abnormalities suggestive of malignancy.

Figure 1. A moderately differentiated adenocarcinoma within the wall of a porcelain gallbladder (Hematoxylin & eosin stain x400)

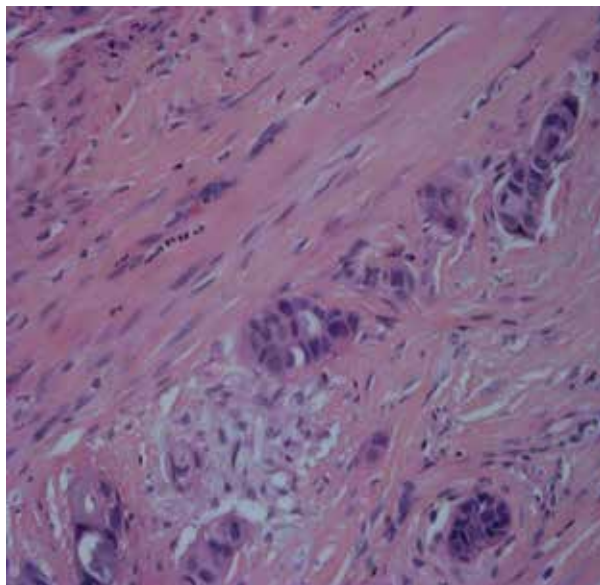
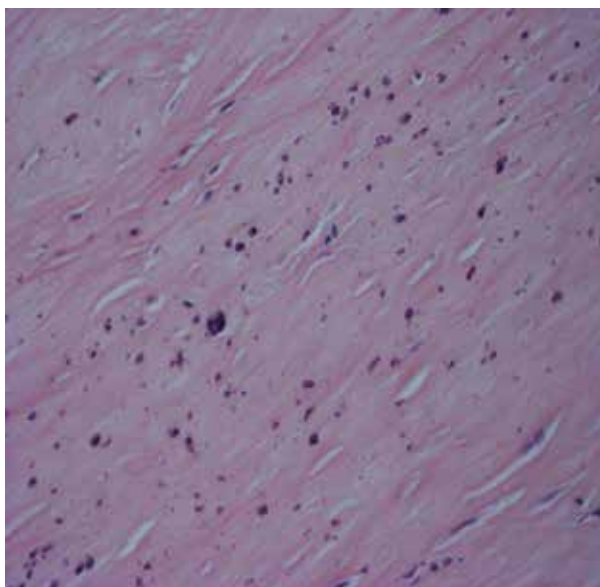


Figure 2. Dense fibrosis with numerous minute calcifications, constituting the wall of the “porcelain gallbladder” (Hematoxylin & eosin stain x400)



She had an uneventful postoperative course and went home on the fourth postoperative day in good condition. Histological examination of the GB specimen revealed a moderately differentiated adenocarcinoma within a porcelain GB [Figures 1 and 2]. The tumor infiltrated the muscularis propria layer. No vascular invasion was identified. Surgical margins were free of tumor.

She was referred for an abdominal computed tomography (CT) scan, which showed no evidence of metastatic disease. One month later, she underwent another operation: laparoscopic ultrasound evaluation and open partial hepatectomy of the GB bed, lymph node dissection of the hepatoduodenal ligament, and resection of the port sites. Several specimens sent for intraoperative pathological examination were all negative.

The postoperative course of the second operation was uneventful. No adjuvant therapy was administered. Six months later, CT of the abdomen showed neither a liver mass nor lymphadenopathy. To date, 55 months after the surgery, the patient continues to be free of tumor.

PATIENT 2

A 60 year old obese female patient (BMI 47) underwent LSG with a simultaneous diaphragmatic hernia repair and LC. Physical examination did not indicate any abnormal findings. The patient's comorbidities included hyperlipidemia, low back pain and fatty liver. As part of her preoperative workup, she underwent upper gastrointestinal series which revealed a small diaphragmatic hernia, and ultrasound of the abdomen which showed a fatty liver and a distended GB with multiple large stones. The GB wall was within normal limits. Routine laboratory testing (complete blood count and serum chemistry panel) revealed only hyperlipidemia.

Laparoscopy failed to disclose any visual evidence of significant abnormalities. The gallbladder was very large and was packed with multiple big stones. Surgery was uneventful, and no intraoperative mishaps were recorded. Her postoperative course was uneventful and the patient was discharged on postoperative day 4.

Histological examination of the GB specimen revealed a poorly differentiated adenocarcinoma with scattered signet ring cells involving the entire GB wall and infiltrating into the surrounding connective tissue serosa. The proximal surgical margin was involved. Tumor cells were immunopositive for CKMNF116, CK7, CK20, CK19, vimentin, CEA and immunonegative for CDX2, WT-1. The morphological and immunohistochemical findings were compatible with a primary adenocarcinoma of the GB [Figures 3 and 4]. Repeat laboratory tests, including liver function tests and amylase, were within normal ranges. Viral hepatitis (hepatitis B and C) profiles were negative.

Surgical exploration was undertaken one month after her LC. At laparotomy, partial resections of the liver bed of the GB with regional lymphadenectomy, excision of cystic stump and excision of the port sites were performed. Multiple specimens were investigated pathologically, intraoperatively, five of which were positive, mandating the resection of the cystic stump in close proximity to the common bile duct until clear margins were achieved.

Figure 3. A poorly differentiated adenocarcinoma Involving gallbladder wall (Hematoxylin & eosin stain x400)

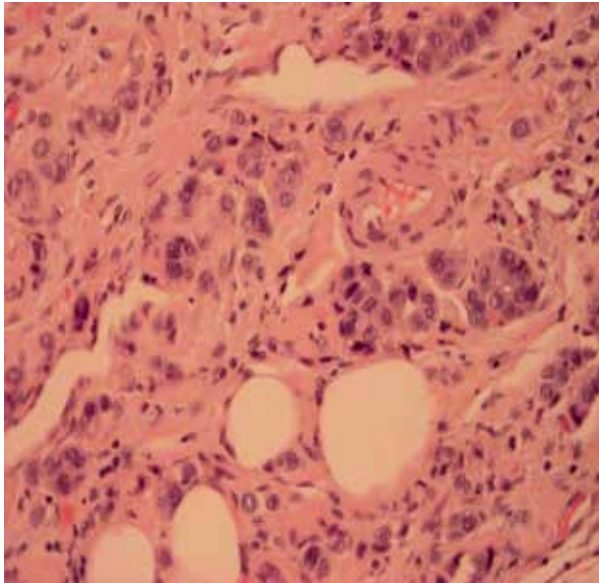
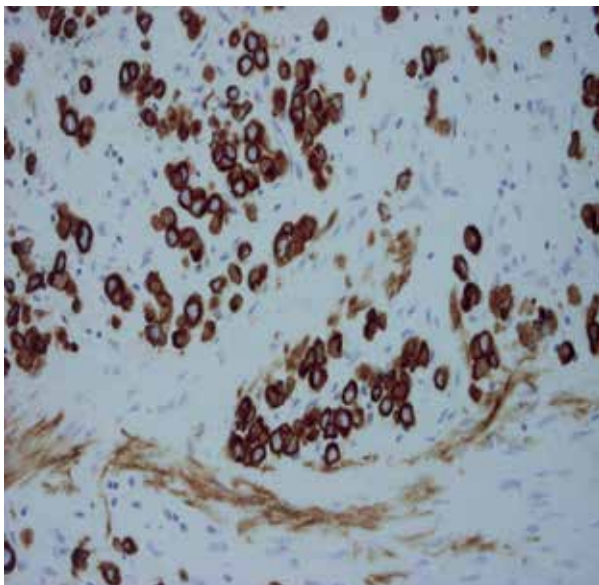


Figure 4. Cytokeratin immunohistochemistry highlighting the same tumor as described in HE sections (Cytokeratin MNF 116 stain x400)



The patient was referred for an abdominal CT scan which showed no evidence of metastatic disease. The liver contained a hypodense region in the GB bed. Fine needle biopsy from this lesion was performed, but no malignancy was found. Positron emission tomography-computed tomography (PET-CT) with 18-fluorodeoxy-glucose demonstrated no hypermetabolic lesions. After her discharge, she was treated

with a chemotherapy regimen as well as radiation therapy.

The patient had an uneventful postoperative and post-chemoradiation course and attended follow-up visits regularly, until she developed a postoperative ventral hernia and had laparoscopic ventral hernia repair with mesh 9 months after surgery. No recurrence was noted at the time of surgery. Her follow-up investigations and liver ultrasound were negative for residual or recurrent disease 18 months after surgery. Twenty months post-LSG+LC the patient developed ascites and was found to have metastatic spread on the omentum. Histology showed signet ring cell adenocarcinoma of biliary origin. The patient was treated with chemotherapy and passed away 38 months after her original surgery.

DISCUSSION

Weight loss surgery with concomitant LC is an accepted option for patients with morbid obesity and symptomatic gallstones. Gallbladder cancer is a relatively rare disease despite being the fifth most common malignant tumor of the gastrointestinal system [3].

The incidence of GB malignancy is low and varies in different parts of the world [4]. It most often manifests in the sixth and seventh decades of life and is more common in women than in men [5-9]. A recent review [10] concluded that GB malignancy should be considered when performing laparoscopic or open cholecystectomy in older, female, Asian or Afro-American patients who have an elevated alkaline phosphatase level. Though much higher when compared to patients without risk factors (0.03%), the incidence of GB malignancy is low (1.4%), even in patients with all of these risk factors.

Israel has a relatively high incidence of GB cancer: 13.8 and 7.5 per 100,000 females and males, respectively. [8] Gallstones are the most common risk factor for GB cancer, increasing the risk of GB cancer four- to fivefold [11]. GB cancer is associated with obesity and increased BMI, particularly among women [2,11-13]. Some small sample studies suggest a positive relationship between obesity and GB cancer [14]. Obesity is a probable cause of gallbladder cancer both directly and indirectly through the propensity for gallstone formation, the strongest known risk factor for this disease [5,15].

A recent meta-analysis of 3288 cholecystectomy cases reported an increased risk of 15% for overweight individuals and 66% for obese individuals compared to normal weight individuals [2]. Obesity may increase risk indirectly by increasing the risk of GB stones, which, in turn, may increase the risk for GB cancer [8]. The association between obesity and gallbladder cancer is stronger in women compared to men [16]. This may be because women are at higher risk of gallstone disease compared to men across all ages [17].

The most common histological type of this neoplasm is adenocarcinoma [7,18]. There are other types of cancer that

can develop in the gallbladder, such as adenosquamous carcinomas, squamous cell carcinomas, small cell carcinomas, and sarcomas, but these are uncommon. There have been several reports of unexpected gallbladder cancer diagnosed after LC [19]. At least three of four people with gallbladder cancer have gallstones when they are diagnosed. Porcelain gallbladder is a condition in which the wall of the gallbladder becomes infiltrated by calcium deposits. This sometimes occurs after chronic inflammation of the gallbladder. Some studies indicate that people with porcelain gallbladder have a high risk of developing GB cancer, but other studies question this.

Barring the occasional cases detected incidentally during LC, which are usually early stage, the prognosis for most patients is poor, especially if the cancer is discovered after symptom initiation [20]. Transabdominal ultrasound, endoscopic ultrasound, CT, PET-CT, magnetic resonance imaging (MRI), and MR cholangio-pancreatography are useful for establishing the diagnosis, as are tumor markers (e.g., Ca 19-9) [21,22].

If GB cancer is incidentally found after cholecystectomy for stone disease, a metastatic workup (usually CT and markers) should be done and, if negative, reoperation is warranted. The goal of reoperation is to remove the GB bed (wedge resection of liver segments 4–5), followed by lymphadenectomy along the hepatoduodenal ligament, the common and proper hepatic arteries, and behind the duodenum and the pancreatic head. Resection of the cystic stump is also required. All specimens should undergo intraoperative pathological examination as their involvement precludes curative resection [23].

A thorough review of the literature yields many reports of GB cancer as an incidental finding in cholecystectomy; however, to the best of our knowledge this is the first such report in the bariatric population that may be at a greater risk for this rare but devastating diagnosis [10].

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