A Rare Condition of Gallbladder Adenocarcinoma Presenting with Acute Cholecystitis Symptoms

Running Title: Gallbladder carcinoma mimicking acute cholecyctitis

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**Clinical Key message:** Although Gallbladder cancer is rare, it is the most common type of biliary tract cancer that could mimic acute cholecystitis symptoms. As it is a poor prognostic and life-threatening condition, diagnosing and treating it as soon as possible is essential.

**Abstract:**

Although gallbladder cancer is a rare malignancy, it is the fifth most common cancer of the digestive tract and the most common in the biliary tract. Gallbladder carcinoma is suspected preoperatively in only 30% of all patients, and the other 70% of cases are diagnosed by a pathologist incidentally. Histologically, the most malignancies are adenocarcinoma; different morphological types have also been described. There are several risk factors for gallbladder cancer, such as gallstone, age, sex, obesity, and underlying disease such as diabetes mellitus type 2. In this case, we will describe acute cholecystitis that has been operated on and postoperative pathology diagnosed gallbladder adenocarcinoma. A 55-years-old female patient presented with suddenly acute abdominal pain, especially right upper quadrant, with a past medical history of hypertension and diabetes mellitus type 2 who underwent open cholecystectomy for suspension of cholecystitis. After surgery, it was found adenocarcinoma by pathology investigation. As the outcome of gallbladder carcinoma is very poor, paying attention to patients with this life-threatening condition is critical.

**Introduction**:

Gallbladder cancer (GBC) is a rare malignancy with non-specific symptoms and may manifest as acute cholecystitis, but it is the most common malignancy in the biliary tract [1]

Gallbladder carcinoma is the fifth most common neoplasm of the digestive tract, and the occurrence probability of GBC is 3 per 100000 people [2]. 70% of all patients with gallbladder carcinoma are diagnosed postoperatively [3].

The gallbladder carcinoma and cholecystitis showed no significant differences in clinical symptoms such as abdominal pain, fever, and jaundice, and other clinical findings such as serum total bilirubin level, leukocyte count, percentage of segmented leukocytes, presence of gallstones, and CT features of pericholecystic stranding/fluid and focally increased enhancement of adjacent liver [4].

Gallbladder cancer has many risk factors, but the main risk factor is the presence of gallstones, which are associated with some environmental factors such as a sedentary lifestyle and a high-fat diet. Other risk factors such as autoimmune disorders and bacterial, parasitic, and fungal infections have also been described [5]. Increasing stone size elevates the risk of developing gallbladder cancer. Gallstones larger than 3 cm are associated with a greater than tenfold increased risk of cancer than small gallstones [3]. Unfortunately, gallbladder cancer outcome is poor, and less than 5% of patients live more than five years [6]. So, it is crucial to diagnose and treat this life-threatening condition as soon as possible.

In this case, a 55-year-old woman presented to the surgical ward with symptoms of acute cholecystitis and gallbladder adenocarcinoma diagnosed postoperatively.

**Case presentation:**

A 55-year-old female presented to the surgical emergency department with a history of acute constant right upper quadrant abdominal pain that spread to the back, which was started just one day before hospitalization. The pain was getting worse with feeding. The pain started suddenly and was not positional. The patient had nausea, vomiting, and anorexia and had no other complaints. The patient had stable vital signs at the time of admission to the emergency ward. RUQ tenderness without rebound tenderness and guarding were found during the abdominal examination, and the murphy's sign was positive (Murphy's sign is elicited in patients with acute cholecystitis by asking the patient to take in and hold a deep breath while palpating the subcostal region." Murphy's sign is performed by palpating the subcostal region during inspiration. If pain is elicited and the patient suddenly stops their inspiratory effort, a positive Murphy's sign has been elicited [7].)

Her past medical history represented that she had hypertension and DM type 2 for five years. The patient took Losartan 25 mg and Metformin 500 mg twice daily.

She was admitted to the surgical ward for more investigation. The patient was asked to do an Upright chest X-ray and supine abdominal X-ray, which were unrevealing, as can be seen in Figures 1 and 2. she was also asked to do abdominal sonography. Abdominal sonography demonstrated anteroposterior diameter increases and wall-thickening of the gallbladder. Also, the image of two stones with dimensions of 6 and 7 mm and a gallbladder containing compacted sludge was seen, as can be seen in Figure 3.

Spiral abdominal and pelvic CT scan with IV contrast were performed for more investigation. In the abdominal CT scan with IV contrast, the evidence of dilation of bile ducts containing gas (pneumobilia) along with soft tissue density at the bifurcation of the central duct to an approximate size of 12\*14 was seen. In addition, there was evidence of increased thickness of the gallbladder wall and stones and gas within the gallbladder. Focal distribution of the gallbladder wall in the fundus region in the anterior part and surrounding stranding is evident without free fluid in the abdomen. There was evidence of slight enhancement in the liver parenchyma adjacent to the gallbladder.

All the blood test analyses at the emergency department were in the normal range, but one day after hospitalization, leukocytosis (white blood cell= 13500 g/dl with a neutrophilia ratio of 79%) was seen.

Due to suspicion of cholecystitis and according to the clinical presentations and the result of blood tests and imaging reports, the patient underwent an operation. After opening the patient's abdomen, there were diffuse adhesions in the abdominal area, and after separating the adhesions, the gallbladder was removed, which was full of gas and necrosis, and a tumoral mass was seen in the body of the gallbladder. Finally, the patient was implanted with a drain, the abdomen was closed, and the gallbladder was sent to the pathology lab for more investigation. After the operation, the patient had a proper recovery and was transferred to the ward. Appropriate and imperative treatments were started for four days. After tolerating PO and defecation, the patient was discharged from the surgical service in good general condition.

The microscopic investigation of the tissue demonstrated a gallbladder wall involved by a malignant neoplasm composed of atypical epithelial cells with pleomorphic and clear to eosinophilic arranged as glands, cribriform structures, and sheets. Microscopic views of the tissue can be seen in Figures 4 and 5.

Also, the pathology report revealed that the gallbladder involved an adenocarcinoma tumor, moderately differentiated in the fundus, body, and neck, measuring 8 in 8 in 1 cm. The pathological stage of the tumor was PT3NxMx, and perineural and lymphovascular invasion were not seen. The liver parenchymal margin was free from the tumor, but the tumor focally involved the cystic duct margin. The patient is in good condition after six months of follow-up.

**Discussion:**

Gall bladder cancer (GBC) is an uncommon malignancy and may manifest as acute cholecystitis. GBC has a dismal prognosis, and the majority of the cases are asymptomatic and are incidentally diagnosed during gallstone exploration or after cholecystectomy is performed for a non-malignant indication [8]. GBD has different types, such as adenocarcinoma, which is the most frequent type and contains approximately 80 to 97% of all cases, squamous-cell, adenosquamous-cell, papillary, small cell carcinoma, and sarcoma [2].

Although different cases have been published about the patient with gallbladder adenocarcinoma who presented with symptoms of acute cholecystitis, we have reported another case in this article due to the importance of this issue, poor precognition, and non-exclusive clinical presentation in compression with cholecystitis.

There are several risk factors to increase the possibility of GBC, such as gallstones, concrements which means biliary lithiasis in the gallbladder and biliary ducts, increasing stone size, type of concrement, and chronic inflammation by causing DNA damage. Gallstones are one of the most critical risk factors for gallbladder cancer, so stones larger than 3 cm increase the probability of GBC incidence by ten times compared to stones smaller than 3 cm [9]. The genetic alterations that occur in the gallbladder wall are important for understanding cancer development, and there is also an interesting correlation between risk factors and the histological cancer type. Obesity, metabolic syndrome, and diabetes mellitus are other risk factors. Different studies have shown the importance of diabetes in increasing the probability of GBC [10,11]. The other risk factor is age and sex. Studies showed that the only digestive system cancer that is more common in women is GBC compared to other digestive system cancer. On the other hand, the risk of gallbladder carcinoma increases with age. With increasing age, the probability of a diagnosis of GBC and the mortality rate also increases. GBC is common after 65 years old [12,13].

According to the American Cancer Society report, the 5-year-survival rate of GBC is according to the stage of cancer and could be different from 66% in localized cancer to just 2 % in patients with distant metastasis [14]. This point shows the importance of diagnosis in the early stages.

Several imaging methods could help us to evaluate the gallbladder in patients with suspicion of cholecystitis or GBC, such as ultrasonography, computed tomography (CT) scan, and magnetic resonance imaging (MRI). A positron emission tomography (PET) scan could be useful in the persistence of distant metastasis. The first and most common method is ultrasonography [13].

CT scan demonstration of focal gallbladder wall thickening, intraluminal masses, small gallbladder with diffuse wall thickening, and enlarged regional lymph nodes suggest concurrent gallbladder carcinoma, especially in a female patient presenting with acute cholecystitis symptoms [4]. In this case, according to the CT scan, the patient underwent surgery with suspicion of GBC.

The surgical team can do surgery in an open or laparoscopic way. Different studies showed that gallbladder carcinoma is found during 0.2%-3% of all open cholecystectomies. On the other hand, during 0.09%-2% of all laparoscopic cholecystectomies, GBC was found. So, it can be concluded that gallbladder carcinoma is an infrequent occurrence and can be considered a rare phenomenon

[12]. The gallbladder is currently removed laparoscopically in more than 75% of cases [6]. Consequently, when GBC is suspected preoperatively, an open technique is recommended for performing a radical cholecystectomy [15].

In this article, a case of gallbladder adenocarcinoma was presented with acute cholecystitis in a female patient with a past medical history of diabetes Mellitus type 2 and hypertension. CT scan showed focal distribution in the gallbladder, the patient underwent open cholecystectomy due to the suspicion of gallbladder cancer before surgery, and post-operative pathology of the gallbladder had been presented as adenocarcinoma as the final diagnosis.

**Conclusions:**

There are several risk factors for GBC, and one of the most important is gallbladder stones and underlying disease, especially DM type 2. For patients with symptoms of cholecystitis, physical examination singly does not help differentiate gallbladder cancer from cholecystitis. For patients with risk factors for gallbladder cancer, it is essential to consider GBC an important differential diagnosis due to its poor prognosis. Every patient with cholecystitis symptoms should undergo ultrasonography and CT scan procedure. Clinical examinations and imaging findings could help doctors evaluate and diagnose the patient's disease. Choosing the best way between different surgical techniques depends on when the surgical team suspects cancer.

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Figures:

1. Upright Chest X-ray
2. Supine Abdominal X-ray
3. Abdominal CT scan with IV contrast:

The green arrow shows the gallbladder wall thickening. The red arrow shows the pneumobilia sign

1. The microscopic view of the gallbladder tissue
2. The microscopic view of the gallbladder tissue