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Case Report

Asymptomatic gangrenous cholecystitis diagnosed using contrast-enhanced ultrasonography in a patient with pancreatic cancer^{☆,☆☆}

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ABSTRACT

A 72-year-old female without abdominal symptoms visited our hospital for routine follow-up while undergoing pancreatic cancer treatment (using TS-1). Her vital signs were normal, and her abdomen was soft and non-tender. Blood test revealed elevated C-reactive protein levels with normal white blood cell count. Computed tomography was performed for follow-up of pancreatic cancer. Contrast-enhanced computed tomography showed partial discontinuity and irregular thickness of the gallbladder wall; however, a definitive diagnosis was not obtained due to unclear imaging. Contrast-enhanced transabdominal ultrasonography revealed intraluminal membranes in the gallbladder and a perfusion defect at the bottom, indicating gangrenous cholecystitis. Surgical resection was performed, and pathological examination showed severe necrosis of the gallbladder wall, consistent with the findings of contrast-enhanced transabdominal ultrasonography.

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Introduction

Gangrenous cholecystitis (GC) was first described in 1894, and is defined as a severe form of acute cholecystitis (AC) with ischemia and necrosis of the gallbladder wall [1]. The prevalence of GC in AC has been reported to be 2%-40% [2]. Since this condition leads to life-threatening complications such as perforation, abscess formation, and peritonitis [3], leading to high mortality [2], accurate diagnosis and prompt surgical treatment are required. These patients generally present with intense abdominal symptoms such as abdominal pain; however, previous studies have reported that several patients with diabetes mellitus (DM) [4,5] and older patients [6] can develop GC without severe abdominal symptoms.

GC can be suspected based on clinical findings including abdominal pain, fever, and inflammatory markers detected in blood tests, and diagnosed by computed tomography (CT) [7], transabdominal ultrasonography (US) [8,9], and magnetic resonance cholangiopancreatography [10,11]. Specific findings of GC include wall projections into the lumen, intraluminal membranes, and decreased enhancement of the gallbladder wall [7–11].

DM, cardiovascular disease (CVD), white blood cell count (WBC) $\geq 15,000$ cells/ μL at diagnosis, and increased age are known risk factors of GC [12,13]. Despite several predictive factors and diagnostic options, preoperative diagnosis of GC is difficult partly due to its atypical presentation [14] and less frequently presented characteristic findings such as intraluminal membranes [15]. Moreover, we have occasionally encountered cases in which contrast media cannot be adopted due to renal dysfunction or allergic reactions, resulting in inadequate imaging information for the diagnosis of GC.

Surgical treatment is mainly required for GC to avoid fatal complications, although the suitability of laparoscopic or open cholecystectomy is still controversial [2]. In this report, we present a rare case of GC without common risk factors and which did not demonstrate the typical clinical features of GC. Furthermore, we reviewed published case reports of GC without abdominal symptoms by searching for these on PubMed/MEDLINE at the end of October 2021 using the following terms: (“gangrenous cholecystitis” or “necrotizing cholecystitis”) AND (“case report” or “case”). The inclusion criteria were as follows: (1) case reports describing the clinical course from admission to treatment; (2) cases without abdominal pain on admission; and (3) full articles with abstracts and reports written in English.

Case report

A 72-year-old female visited our institution for a routine follow-up of pancreatic cancer treatment. She was orally taking TS-1, without severe complications such as neuropathy, and was not taking opioids. She was a non-smoker and had no history of smoking, DM, or CVD. Her vital signs on admission were as follows: temperature, 36.1°C; blood pressure, 80/45 mm Hg; heart rate 100 beats/min; respiratory rate, 16 breaths/min; and O_2 saturation in room air, 97%. On

physical examination, conjunctival icterus was not detected. Her abdomen was soft and non-tender. The blood test revealed a normal WBC count (5870 cells/ μL), elevated C-reactive protein level (8.63 mg/dL), as well as a normal liver function test (aspartate aminotransferase level, 20 U/L and alanine aminotransferase level, 21 U/L) and creatinine level (0.52 mg/dL) (Table 1).

Contrast-enhanced computed tomography (CECT) revealed irregular thickness and partial defect of the gallbladder wall by the contrast agent in the wall. Fluid appeared to project into the liver. An enhanced area of the liver surrounding the gallbladder was detected in the early phase, indicating acute inflammation. A biliary stent (10Fr.-7cm Double Layer Biliary Stent) was placed in the common bile duct, and dilatation was not detected (Fig. 1). GC was suspected based on the above findings; however, we could not reach a definitive diagnosis due to insufficient imaging. US revealed intraluminal membranes in the gallbladder. Contrast-enhanced transabdominal ultrasonography (CEUS) with Sonazoid showed perfusion defects at the bottom of the gallbladder. A low echoic area without perfusion indicating an abscess and high echoic findings indicating parenteral air were not detected around the gallbladder (Fig. 2).

Based on these findings, we diagnosed the patient's condition as GC, and surgical treatment was performed. Initially, laparoscopic cholecystectomy was attempted; however, after detecting intense adhesion of the gallbladder to the lesser omentum, the laparoscopic approach was converted to open cholecystectomy, resulting in complete excision of the gallbladder. A calculus was incarcerated in the cystic duct. Pathological findings showed infiltration of inflammatory cells and severe necrosis of the gallbladder wall, which was consistent with GC. No malignant cells were found in the gallbladder (Fig. 3). The postoperative course was uneventful, and 14 days after surgery, the patient was discharged from our hospital.

Discussion

To our knowledge, this is the first report of asymptomatic GC diagnosed using contrast-enhanced ultrasonography in a patient with advanced pancreatic cancer. In this patient, besides asymptomatic status, typical risk factors of GC such as DM, CVD, abnormal liver function test (aspartate aminotransferase and alanine aminotransferase), and high WBC count $> 15,000$ cells/ μL were not observed [13]. Thus, without an imaging test, it would have been difficult to predict the presence of GC.

In cancer patients, similar to our case, the risk of cholecystitis has been proven to be higher than that in patients without cancer due to malnutrition, leading to gallstone formation and decreased immunity to bacterial infections [16]. The conditions which require placement of a biliary stent, especially pancreatic cancer and cholangiocarcinoma, can increase the risk of subsequent cholecystitis [17]. However, whether cholecystitis patients with cancer have a higher risk of progression to GC remains unclear. Therefore, further accumulation of cases and large-scale investigations are required.

In general, patients with GC present with severe symptoms, including abdominal pain and high fever [2]. However,

Table 1 – Laboratory findings on admission.

Hematology	
WBC	5870/ μ L
RBC	3.24×10^6 / μ L
Hb	9.7 g/dL
Ht	29.9 %
PLT	16.4×10^4 / μ L
Biochemistry	
TP	6.1 g/dL
Alb	2.6 g/dL
AST	21 IU/L
ALT	20 IU/L
LDH	174 IU/L
ALP	406 IU/L
γ -GTP	42 IU/L
Amy	22 IU/L
Cr	0.52 mg/dL
BUN	13 mg/dL
Na	139 mEq/L
K	3.8 mEq/L
Cl	105 mEq/L
Ca	8.2 mg/dL
IP	3.2 mg/dL
Mg	1.9 mg/dL
Glu	119 mg/dL
CRP	8.63 mg/dL

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; PLT, platelets; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ -GTP, gamma-glutamyl transpeptidase; Amy, amylase; Cr, creatinine; BUN, blood urea nitrogen; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; IP, inorganic phosphorus; Mg, magnesium; Glu, glucose; CRP, C-reactive protein.



Fig. 1 – Findings of the contrast-enhanced computed tomography. Irregular thickness and partial discontinuity of the gallbladder wall with projection of fluid into the liver was observed. (A) Axial image. (B) Coronal image. (C) Sagittal image.

we found a few asymptomatic cases of GC in literature, which are summarized in Table 2. The youngest case was of a 42-year-old female, and all these patients had DM. Additionally, a history of neuropathy and CVD and an elevated WBC count in the blood test were reported in these patients [18,19]. In contrast, the clinical background of our case was not relevant to the known risk factors of GC, except for older age. Therefore, physicians should keep in mind that GC can occur even in patients without risk factors and typical symptoms, and imaging tests should be conducted when patients with carcinoma exhibit unexplained inflammatory findings on blood tests.

Diagnosis of GC is often difficult because typical findings are found only in a small number of GC patients [20]. In previously reported cases, CT, hepatobiliary iminodiacetic acid scan, and US without contrast were adopted for the diagnosis of GC. CT is considered the standard method for the diagnosis of GC. CT findings such as gallbladder distention >4.0 cm, mural striation, and decreased mural enhancement are key findings in the detection of GC [7]. In our patient, due to the lack of these findings in CECT, only the CT findings could not reach a definite diagnosis of GC, and CEUS was able to complete the diagnosis. This can stem from the difficulty of evaluating

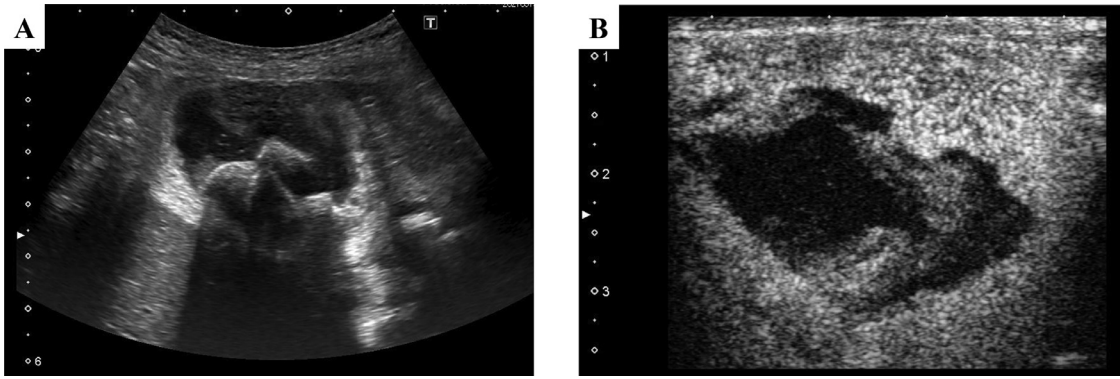


Fig. 2 – Contrast-enhanced transabdominal ultrasonography revealed (A) intraluminal membranes and (B) perfusion defects at the bottom of the gallbladder.

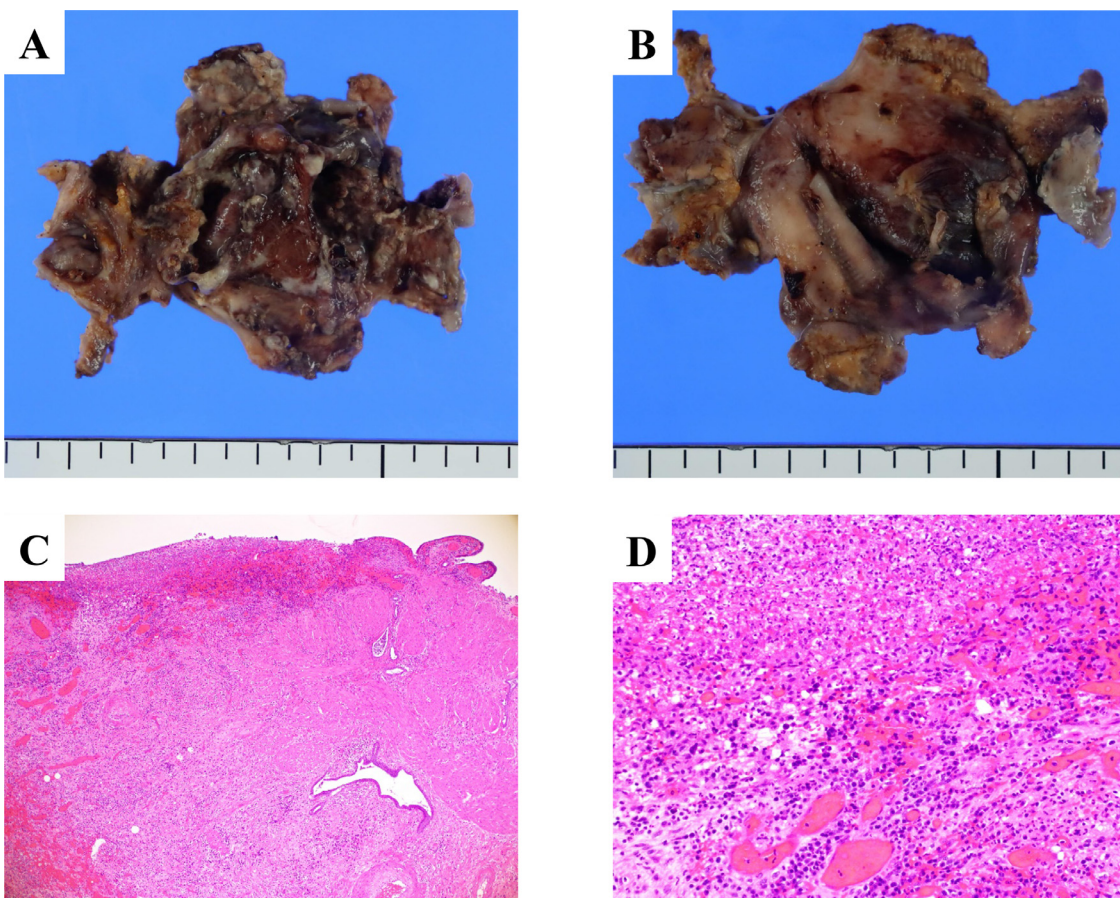


Fig. 3 – (A, B) Macroscopic findings of the removed gallbladder. Pathological findings showed infiltration of inflammatory cells and severe necrosis of the gallbladder wall. No malignant cells were found in the gallbladder. (C) Hematoxylin and eosin staining under x 40 magnification and (D) x 200 magnification.

the enhancement of the gallbladder wall due to its thinness. CECT has been reported to show adequate specificity (96.0%–100.0%) for the diagnosis of GC; however, it has a low sensitivity (29.3%–70.6%) [8]. On the contrary, CEUS is proven to have a sensitivity of 85%–91% and a specificity of 67.5%–84.8% [9]. This higher percentage mainly comes from the greater spatial resolution of US compared to CT and magnetic resonance

imaging, as well as the proximity of the gallbladder from the body surface. In our patient, a perfusion defect was confirmed by CEUS, which reported 100% specificity and a positive predictive value [8]. As a result, diagnosis was confirmed, and the patient immediately underwent surgical resection. In addition to its higher diagnostic value, CEUS has several advantages compared to CECT, such as CEUS can be performed in patients

Table 2 – Summary of previous case reports and the characteristics of each patient with asymptomatic gangrenous cholecystitis.

Case report author (year)	Age	Sex	Country	Comorbidity	Symptoms	Relevant diagnostic method	Surgical treatment	Outcome
Grant et al. (2002) (17)	42	F	Australia	Type 2 diabetes mellitus and renal disease	None (examination for renal disease)	Transabdominal ultrasonography	Laparoscopic cholecystectomy	Recurrence after 3 days
Nidimusili et al. (2013) (18)	66	M	United States	Type 2 diabetes mellitus and hypertension	Discomfort on the left side of the chest	Computed tomography (distended gallbladder and air bubbles in the gallbladder neck)	Laparoscopic cholecystectomy	Uneventful
Mehrzhad et al. (2018) (4)	83	M	United States	Type 2 diabetes mellitus	Nausea	Hepatobiliary iminodiacetic acid scan	Laparoscopic cholecystectomy	Uneventful
Our case (2022)	72	F	Japan	Pancreatic cancer	None (routine check-up for chemotherapy)	Contrast-enhanced transabdominal ultrasonography	Surgical resection	Uneventful

M, male; F, female.

with renal dysfunction or allergic reactions to iodinated contrast agents, and CEUS can be performed without radiation exposure. Furthermore, the cost of equipment for CEUS is much lower than that required for CECT.

In terms of the surgical approach for GC, some group recommended laparoscopic cholecystectomy due to the short hospital stay, and others suggested that open cholecystectomy can still be an initial option due to its higher safety [21]. Based on these conditions, the most suitable strategy should be an initial approach using laparoscopic cholecystectomy, and if necessary, conversion to open surgery should be made by rapid judgment [22]. Laparoscopic cholecystectomy was performed in previous cases and was also attempted initially for our case. However, the gallbladder of our patient was removed using the open approach because of severe adhesion.

In conclusion, we present an asymptomatic case of GC without severe complications of GC, such as perforation. GC can be considered as a differential diagnosis for mild abdominal symptoms; however, GC can also occur without any symptoms in patients with pancreatic cancer. Thus, CEUS is one of the useful modalities for making a definite diagnosis of GC.

Patient consent statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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