

Gangrenous Cholecystitis as a Potential Complication of COVID-19: A Case Report

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ABSTRACT: While primarily a respiratory disease, COVID-19 can affect several organ systems and has been recently linked to cases of acalculous cholecystitis. We present a previously healthy elderly patient who presented to the emergency department with sepsis and was found to have COVID-19 after initially testing negative on PCR, along with suspected concomitant acalculous gangrenous cholecystitis. The patient passed away before any surgical intervention could be made. This case aims to discuss the potential relationship between acalculous cholecystitis and COVID-19.

KEYWORDS: COVID-19, gangrenous cholecystitis, SARS-CoV-2, acalculous cholecystitis

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Background

On March 11, the World Health Organization (WHO) declared COVID-19 as a pandemic disease. Clinical manifestations of the disease are broad and can include fever, cough, chest pain, and gastrointestinal symptoms including diarrhea, vomiting, and abdominal pain.¹ Recently, reports of acute cholecystitis associated with COVID-19 pneumonia have emerged in the literature.^{2,3}

We report a case of an elderly female who presented with generalized abdominal pain in the clinical setting of sepsis, who had an initial negative COVID-19 PCR with a positive repeat and was found to have acute gangrenous cholecystitis but passed away before proper surgical intervention could be made. We therefore explore acalculous cholecystitis as a potential complication of COVID-19.

Case Presentation

A previously healthy 84-year-old Caucasian female (height of 165 cm and weight of 45 kg) was brought to the emergency department for 2 days of generalized abdominal pain, vomiting (non-bloody and non-bilious), and diarrhea (non-bloody and non-mucoid) as reported by family members. She had no prior symptoms, respiratory or otherwise, and was afebrile prior to the day of presentation. Upon presentation, patient had altered general status, was in respiratory distress, tachypneic, and was using her accessory muscles. She was febrile (39.5°C buccal), tachycardic (heart rate: 130–140 beats per minute), tachypneic (respiratory rate: 37), in desaturation (O₂ saturation: 70% on room air), and hypotensive (systolic blood pressure: 70 mmHg). Arterial blood gases taken showed a primary metabolic acidosis with an anion gap of 23 (Table 1). Her oxygen saturation increased to 95% following the use of a non-rebreather face-mask. Hydration with a total of 3 L normal saline increased her

systolic blood pressure to 120 mmHg. On reexamination, patient had right upper quadrant tenderness with a positive Murphy's sign. Two sets of blood cultures and urine cultures were taken after which the patient was given 1 g Amikacin, 1 g Vancomycin, and was started on intravenous Tazocin 4.5 g every 6 hours. Due to the lack of available beds in the intensive care unit, patient remained in the emergency department.

COVID-19 PCR test was taken through a nasopharyngeal swab and the specimen was negative for SARS-CoV-2 (Figure 1). Inflammatory markers were significantly elevated with a C-reactive protein of 50, lactate dehydrogenase 240, ferritin 271.6, fibrinogen 1017.15, and erythrocyte sedimentation rate 86. Patient was lymphopenic with an absolute lymphocytic count of 357. Patient also had elevated amylase (578) and bilirubin (direct 1.65/total 2.29) but normal aspartate aminotransferase and alanine aminotransferase (Table 2).

CT chest-abdomen-pelvis done revealed extensive patchy consolidations with air bronchograms and ground glass opacities, involving predominantly the right upper lobe and both lower lobes suggestive COVID-19 pneumonia (Figure 2). The gallbladder was markedly distended with a transverse diameter reaching 4.6 cm, with an enhancing wall showing focal defects compatible with partial necrosis, surrounded by fat stranding and peri-vesicular fluid. There were 2 adjacent hypodensities in the liver the largest measuring 1.2 cm × 1 cm suggestive of pericholecystic abscesses (Figure 3). The above findings were suggestive of acute ischemic gangrenous cholecystitis; however, an abdominal ultrasound was not done for confirmation.

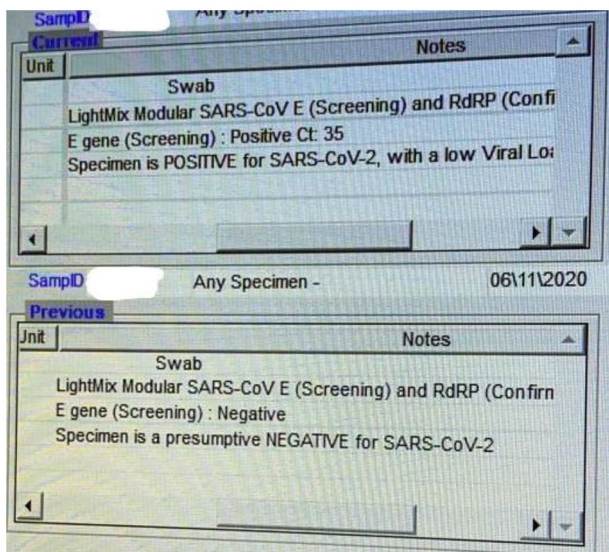
The patient was scheduled for percutaneous drainage and a repeat COVID-19 PCR was done. Overnight, she became hypotensive again and was refractory to IV fluids. Dopamine was started which successfully elevated her systolic blood pressure. However, the next morning, she deteriorated again and



Table 1. Arterial blood gases taken on patient presentation.

	NORMAL VALUE	PATIENT'S VALUE
pH	7.35-7.45	7.37
pCO ₂ (mmHg)	35-45	37.4
pO ₂ (mmHg)	75-100	40
HCO ₃ ⁻ (mmHg)	22-26	21.7
SO ₂ (%)	98-100	70
Anion gap (mEq/L)	<11	23

Values highlighted in bold-italic are considered abnormal.

**Figure 1.** RT-PCR for SARS-CoV-2 done on 7/11/2020 (positive) and 6/11/2020 (negative).

became hypotensive (systolic blood pressure: 50 mmHg) and desaturated (oxygen saturation: 70% on non-rebreather face mask). She was put on a double oxygen source: non-rebreather face mask and nasal cannula high flow oxygen. Saturation did not improve, and patient remained hypotensive despite increasing doses of dopamine. She was immediately intubated after which she went into cardio-pulmonary arrest. Resuscitation failed and she was pronounced dead shortly thereafter. The repeat PCR for COVID-19 turned out to be positive later in the day (Figure 1), and the blood cultures and urine culture that were taken turned out negative.

Discussion

Acute gangrenous cholecystitis as a complication of COVID-19 has been previously described in 1 case,⁴ and our case highlights a similar relationship in a patient with COVID-19 who, however, initially complained of gastrointestinal symptoms and was found to be septic and hypoxic with CT abdomen suggesting the concomitant presence of gangrenous cholecystitis.

Table 2. Blood tests taken in the Emergency Department on patient presentation.

	LABORATORY REFERENCE VALUE	PATIENT VALUE
White blood cell count (10 ⁹ /L)	4.5-11	1.94
Neutrophils (%)	40-70	70.8
Lymphocytes (%)	20-40	18.4
Lymphocytic count (per mm ³)	1000-4000	357
Platelets ($n \times 10^3/\mu\text{L}$)	150-450	130
INR	<1.1	1.24
Amylase (U/L)	40-130	578
Total Bilirubin (mg/dL)	<1.2	2.29
Direct bilirubin (mg/dL)	<0.3	1.65
CRP (mg/L)	<10	50
ESR (mm/hr)	<30	86
Lactate dehydrogenase (U/L)	<200	240
Ferritin (ng/mL)	<120	271.6
Fibrinogen (mg/dL)	<400	1017
Creatinine (mg/dL)	<1.2	0.86
Urea (mg/dL)	<20	76
Sodium (mEq/L)	135-145	142
Potassium (mEq/L)	3.5-4.5	4.1
Chloride (mEq/L)	95-105	103
Bicarbonate (mEq/L)	23-30	20.4
Alanine aminotransferase (U/L)	<55	14
Aspartate aminotransferase (U/L)	<45	28
Alkaline phosphatase (U/L)	<100	93
GGT (U/L)	<40	22
Troponin (ng/mL)	<0.01	0.018

Values highlighted in bold-italic are considered abnormal.

The most common clinical manifestations of COVID-19 range from fever, fatigue, cough, and dyspnea in mild cases to acute respiratory distress syndrome in severe cases.¹ Gastrointestinal symptoms such as vomiting, diarrhea, or abdominal pain have been reported to precede respiratory symptoms in the early phases of the disease, and carry a worse prognosis.^{5,6} While the patient was brought into the emergency departments for complaints of GI symptoms without any respiratory complaints, she was found to be hypoxic and in

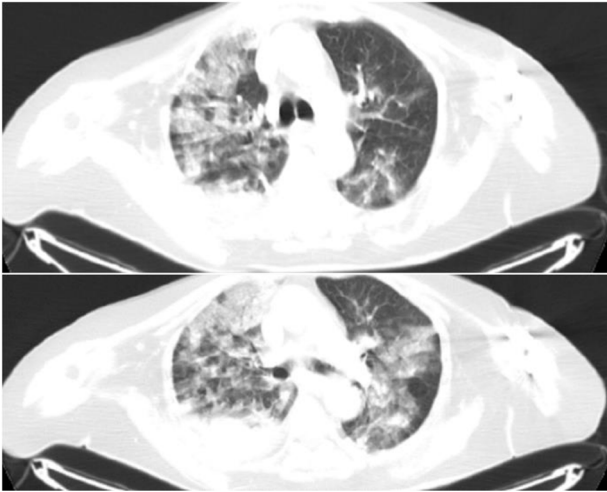


Figure 2. CT chest demonstrating extensive patchy consolidations with air bronchograms and GGOs, involving predominantly the right upper lobe and both lower lobes suggestive of COVID-19 pneumonia.

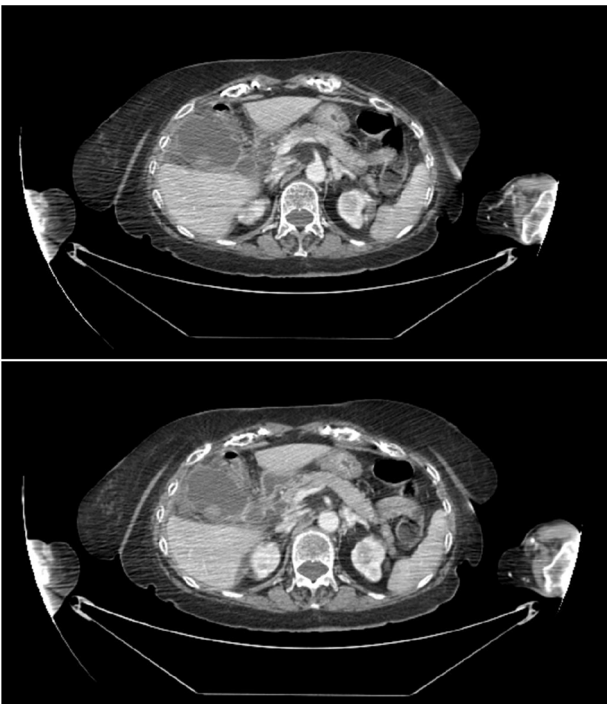


Figure 3. CT abdomen showing a markedly distended gallbladder with a transverse diameter reaching 4.6 cm, with an enhancing wall showing focal defects compatible with partial necrosis, surrounded by fat stranding and peri-vesicular fluid. Two adjacent hypodensities are seen in the liver, the largest measuring 1.2 cm × 1 cm, suggestive of pericholecystic abscesses.

need of O₂-supplementation, and therefore whether her GI symptoms truly preceded any respiratory manifestations is debatable. Although the initial PCR was negative, chest CT was strongly indicative of COVID-19 and the repeat PCR turned positive with a low viral load. Findings on CT abdomen were suggestive of acute gangrenous cholecystitis but

confirmation with ultrasound was not made. The surgical team that was consulted recommended percutaneous gallbladder drainage, but the patient went into arrest and could not be resuscitated and sampling the gallbladder wall for SARS-CoV-2 was not possible.

Recent data has shown tropism of the SARS-CoV-2 virus to cells of the lungs and liver, which exhibit angiotensin-converting enzyme 2 (ACE2) receptors that allow cell entry of the virus.⁷ ACE2 expression has been found to be much higher in bile duct cells than that in liver cells, and comparable to that of alveolar type 2 cells in the lungs, suggesting liver injury occurs in COVID-19 patients due to damage to bile duct cells.⁸ A recent case report described the detection of SARS-CoV-2 through RT-PCR in a bile specimen of a patient with severe COVID-19 who was found to have bile duct obstruction.⁹ Of the 4 reported cases of COVID-19 associated acalculous cholecystitis, two reported the presence SARS-CoV-2 in the gallbladder via RT-PCR.² The characteristics of each case are summarized in the table below (Table 3). A clinical trial regarding the risk factors for necrotic cholecystitis in the COVID-19 pandemic is currently underway by Poissy-Saint Germain Hospital and will likely clarify the relationship between COVID-19 and cholecystitis and the pathophysiology involved.¹⁰ In June 2020, recommendations were released to manage cases of cholecystitis with laparoscopic cholecystectomy when possible, even in the COVID-19 era.¹¹ As previous cases have shown, both surgical or conservative management of acalculous cholecystitis associated with COVID-19 is possible depending on the severity of the disease and patient's hemodynamic stability. However, our case remains unclear as to whether the cholecystitis was directly caused by SARS-CoV-2's tropism to bile duct cells or if it was a complication of prolonged hypotension, and whether it was truly acalculous as abdominal ultrasound was not performed for confirmation.

Limitations

The primary limitation of our case report is the lack of RT-PCR testing for SARS-CoV-2 of the bile or gallbladder wall due to the patient passing away before possible surgical intervention. Additionally, since only abdominal CT was done, we could not confirm whether the cholecystitis was acalculous as confirmation requires imaging with abdominal ultrasound.

Conclusion

The mechanism by which COVID-19 can lead to acalculous cholecystitis is still unclear with further studies needed to understand the risk factors associated with developing cholecystitis from COVID-19, and to understand the pathogenesis. Considering that many COVID-19 patients present exclusively with gastrointestinal symptoms, clinicians should broaden their differential and consider testing for SARS-CoV-2 in cases

Table 3. Summary of confirmed COVID-19 associated acalculous cholecystitis cases.

	PATIENT CHARACTERISTICS	INITIAL PRESENTATION AND FINDINGS	PROGRESSION	OUTCOME
Case 1	68-year-old woman previously healthy	Fever, diarrhea, CT chest suggestive of COVID-19	Fever on day 10 of hospitalization, RUQ pain, CT abdomen showed acalculous cholecystitis	PTGD ^a on day 13 in combination with lopinavir/ritonavir and human interferon alfa-1b inhalation, discharge on day 25
Case 2	84-year-old woman previously healthy	Fever, UTI symptoms, and clinical picture of pyelonephritis	Day 3 RUQ pain; Day 5 positive Murphy + elevated CRP, US suggestive of acalculous cholecystitis	Laparoscopic cholecystectomy on day 8, ARDS and death 5d postop.
Case 3	83-year-old man on dialysis for end-stage renal disease with type 2 diabetes, arterial hypertension, and moderate aortic stenosis	Fever	Day 5 RUQ pain, positive Murphy, elevated CRP, US suggestive of acalculous cholecystitis	Conservative management with ceftriaxone and metronidazole, day 6 respiratory symptoms + positive COVID-19 PCR
Case 4	59-year-old male previously healthy	ARDS and SARS-CoV-2 infection confirmed	Day 32 abdominal pain, CT suggestive of acalculous necrotic gangrenous cholecystitis	Laparotomic cholecystectomy, discharge on day 44

^aPercutaneous transhepatic gallbladder drainage.

suggestive of cholecystitis in patients deemed high risk for COVID-19 infection.

Author Contributions

Dr. Walid Alam contributed to writing of the manuscript, literature review, data analysis, and final revision. Dr. Karam Karam contributed to data collection and writing of the manuscript.


Ethics Approval and Consent to Participate

Not applicable. A case report per the University of Balamand IRB (irb@balamand.edu.lb) purposes is a retrospective analysis of 1, 2, or 3 clinical cases. If more than 3 cases are involved in the analytical activity, the activity will constitute “research.” Per the Institutional Review Board of the University of Balamand, all case reports below 4 cases do not require IRB approval as they do not fall into the category of “research.”

Consent for Publication

As the patient’s family do not reside in Lebanon, exhaustive attempts have been made to contact them, but they were unsuccessful. However, the paper has been sufficiently anonymized as to not cause harm to the patient’s family.

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