Case report

Acute acalculous cholecystitis caused by SARS-CoV-2 infection: A case report and literature review

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ARTICLE INFO

Keywords:
Acute acalculous cholecystitis
SARS-CoV-2
COVID-19

ABSTRACT

Background: Emerging data indicate that gastrointestinal disorders, in addition to pulmonary dysfunction, are also hallmarks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Case presentation: A 42-year-old man with maintenance hemodialysis developed high fever and dyspnea. He was positive for SARS-CoV-2 and was diagnosed with pneumonia. After treatment for SARS-CoV-2, his respiratory condition improved. However, he developed right upper quadrant pain with elevated inflammatory markers (white blood cells, 21,160/μL; c-reactive protein, 163.9 mg/L) on the 13th day. Abdominal computed tomography revealed acute acalculous cholecystitis. Percutaneous transhepatic gallbladder drainage (PTGBD) was performed together with antibiotic therapy, which resulted in improvement of symptoms. Laparoscopic cholecystectomy was performed 36 days after PTGBD. Conclusion: We report a rare case of acute acalculous cholecystitis (AAC) following pneumonia caused by SARS-CoV-2 infection. We also conducted a literature search to characterize SARS-CoV-2-related cholecystitis. Infection with SARS-CoV-2 is an important trigger for AAC, and appropriate therapeutic alternatives should be cautiously selected according to individual cases.

1. Background

The outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was named “coronavirus disease (COVID-19)” by the World Health Organization, and it has been a critical blow to the health care and economy worldwide. Since the first diagnosed case of COVID-19 in December 2019, it has spread worldwide with detrimental consequences [1]. Patients infected with SARS-CoV-2 typically present with a variety of respiratory symptoms, ranging from asymptomatic disease to acute respiratory distress syndrome or respiratory failure [2]. In addition to pulmonary dysfunction, recent reports indicate that multiorgan diseases, such as gastrointestinal, cardiovascular, and renal disorders, are also a hallmark of COVID-19 [2]. Several studies have reported that some patients with SARS-CoV-2 present with gastrointestinal symptoms, such as abdominal pain, diarrhea, and vomiting [3]. Additionally, emerging data show that angiotensin-converting enzyme 2 (ACE2), which is known as the major receptor for SARS-CoV-2, is highly expressed in the gastrointestinal tract, biliary tract, pancreas, and liver cells, indicating that abdominal organs can be targeted by SARS-CoV-2 [4]. Therefore, focusing on SARS-CoV-2 as a trigger for abdominal disease will lead to the development of the management of COVID-19. Herein, we report a rare case of COVID-19 pneumonia presenting with acute acalculous cholecystitis. This case report has been written in line with the SCARE criteria [5].

2. Case presentation

The patient was a 42-year-old man undergoing maintenance hemodialysis for renal failure. He presented to his family doctor with a chief complaint of high fever and cough and was found to be positive for SARS-CoV-2 via polymerase chain reaction (PCR) test. Five days after the onset, he was transferred to the emergency department of our hospital owing to decreased oxygen saturation. At the time of admission to our hospital, his body temperature was 38.1 °C, oxygen saturation was <90% on room air, and he complained of severe dyspnea; however, there were no abdominal symptoms. Computed tomography (CT) scan
showed bilateral multifocal peripheral ground-glass opacities, mostly in the lower lungs, which are typical findings for COVID-19 pneumonia. Laboratory evaluation revealed a white blood cell (WBC) count of 6040/μL, hemoglobin of 13.6 g/dL, platelet count of 125 × 10^3/μL, and hepatobiliary and pancreatic enzymes, and coagulation markers were within the normal range. Serum level of C-reactive protein (CRP) (163.9 mg/L) was markedly elevated. Oxygen (4 L/min) was administered, and the patient received antibiotic therapy, steroid (dexamethasone, 6 mg), remdesivir, and subcutaneous heparin. Although the CRP level decreased, his respiratory condition progressively worsened over 3 days with increased oxygen administration (8 L/min by non-rebreather mask), and treatment with steroid pulse (methylprednisolone of 125 mg/day) was administered. Consequently, his respiratory condition gradually improved and he was weaned off oxygen on the fifth day after admission. However, he developed epigastric pain with elevated serum amylase (340 U/L) on the seventh hospital day, and he complained of severe right upper quadrant pain, with elevated WBC count of 21,160/μL, CRP of 143.8 mg/L, and D-dimer of 3.6 μg/mL on the 13th day. CT and abdominal ultrasound showed a significantly enlarged gallbladder, gallbladder wall thickening, and mild pancreatic swelling without gallstones or pancreatic stones. He was diagnosed with moderate grade acute acalculous cholecystitis (AAC) according to the Tokyo Guidelines 2018 [6]. As the patient’s American Society of Anesthesiologists Physical Status was 3 (maintenance hemodialysis for renal failure), percutaneous transhepatic gallbladder drainage (PTGBD) was performed together with antibiotic therapy, resulting in improvement of abdominal pain and normalization of WBC count and CRP. He was discharged from the hospital 1 month after admission, with a PTGBD tube in place. A summary of the clinical course is presented in Fig. 1. To prevent recurrence of cholecystitis, he was confirmed to be negative for SARS-CoV-2 via PCR test, after which we performed laparoscopic cholecystectomy (Lap—C) 36 days after PTGBD. Intraoperative findings revealed that the gallbladder was covered by the greater omentum, and the neck of the gallbladder was displaced toward the hepatic hilum, making it difficult to identify the Calot triangle. Therefore, we performed a retrograde dissection. It was challenging to separate the gallbladder from the liver owing to severe inflammation around the puncture site of the PTGBD tube. The PTGBD tube was intraoperatively removed, and the gallbladder was dissected at the junction of the cystic duct. The postoperative course was uneventful, and the patient was discharged on postoperative day five. Pathological examination revealed that whereas inflammatory cell infiltration was observed especially around the

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**Fig. 1.** Clinical course of the present case. The arrows show the duration of each treatment. PTGBD, percutaneous transhepatic gallbladder drainage.

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**Fig. 2.** Macroscopic and pathological findings of the gallbladder. (a) Resected specimen of the gallbladder. The white arrow shows the penetration site of the PTGBD tube. (b and c) Hematoxylin-eosin-stained sections of the gallbladder. b, Low power field; c, High power field.
Table 1
Reported cases of acute acalculous cholecystitis related to COVID19.

| Case# | Study | Age/Sex | Comorbidity | Onset of AAC | Time-lag (days) | Coagulopathy | Grade | Basis for Grade | Initial treatment | Second treatment | Time-lag (days) | Patient Outcome |
|-------|-------|---------|-------------|--------------|----------------|---------------|-------|----------------|-----------------|-----------------|----------------|----------------|
| 1     | Alhassan, et al. | 40/F | None | Pneumonia→AAC | 14 | Yes | I | Gangrenous cholecystitis | Conservative | | | Discharge |
| 2     | Asti, et al. | 86/F | ND | Pneumonia→AAC | ND | ND | II | Gangrenous cholecystitis | Lap-C | | | ND |
| 3     | 72/M | ND | Pneumonia→AAC | ND | ND | II | Gangrenous cholecystitis | Lap-C | | | ND |
| 4     | 40/M | ND | Pneumonia→AAC | ND | ND | II | Gangrenous cholecystitis | Lap-C | | | ND |
| 5     | Balaphas, et al. | 84/F | ND | AAC→pneumonia | 4 | ND | II | Gangrenous cholecystitis | Conservative | Lap-C | 3 | Multiple organ failure, Death |
| 6     | Bruni, et al. | 83/M | Renal failure | AAC→pneumonia | 1 | ND | II | WBC > 18,000 | Conservative | | | ND |
| 7     | Cirillo, et al. | 59/M | Diabetes, HT | Pneumonia→AAC | 32 | ND | II | WBC > 18,000 | Cholecystectomy | | | Discharge |
| 8     | Hassani, et al. | 65/M | HD, HT | Synchronous | 7 | Yes | II | Perforation | Conservative | | | Discharge |
| 9     | Kahir, et al. | Ul/M | ND | Pneumonia→AAC | 9 | ND | II | Gangrenous cholecystitis | Lap-C | | | ND |
| 10    | Mattone, et al. | 66/M | None | Pneumonia→AAC | 49 | ND | II | Gangrenous cholecystitis | PTGBD | Lap-C | 3 | Discharge |
| 11    | Singh, et al. | 66/M | HD | Synchronous | 9 | ND | Duration of complaints | PTGBD | | | Hospitalization |
| 12    | Ying, et al. | 68/F | None | Pneumonia→AAC | 9 | Yes | ND | Pericholecystic abscess | PTGBD | | | ND |
| 13    | Abaleka, et al. | 76/F | HD, asthma, HT | Synchronous | Yes | II | Gangrenous cholecystitis | Conservative | | | Discharge |
| 14    | Alam, et al. | 84/F | None | Synchronous | Yes | II | WBC > 18,000 | Conservative | Lap-C | >42 | Pneumonia, Death |
| 15    | Rivera-Alonso, et al. | 51/M | None | Synchronous | Yes | II | WBC > 18,000 | PTGBD | Lap-C | 36 | Discharge |
| 16    | Our case | 42/M | Renal failure | Pneumonia→AAC | 18 | Yes | II | WBC > 18,000 | PTGBD | | | Discharge |

AAC, acute acalculous cholecystitis; ND, not described; HD, heart disease; HT, hypertension; WBC, white blood cell.
Lap-c, laparoscopic cholecystectomy; PTGBD, percutaneous transhepatic gallbladder drainage.

a Temporal relationship between AAC and COVID19 pneumonia.

b Time-lag between AAC and pneumonia.

c Coagulopathy at the time of the onset of AAC.

d Severity grading for acute cholecystitis according to Tokyo guidelines 2018.

e Initial treatment within two days of onset.

f Time-lag between initial and second treatments.
when it is caused by SARS-CoV-2 infection. We classified the severity of vascular endothelium, and the attachment of SARS-CoV-2 via ACE2 cells of the lungs [4]. Additionally, ACE2 is highly expressed in the vascular endothelium, and the attachment of SARS-CoV-2 via ACE2 causes endotheliitis, leading to thromboembolism in multiple organs, including the gallbladder [7]. These findings suggest that the hepatobiliary system could be a potential target of SARS-CoV-2. Although the direct interaction between SARS-CoV-2 and AAC, such as the presence of SARS-CoV-2 in the bile, was not examined in our case, given that acalculous cholecystitis typically develops in critically ill or immunosuppressed patients and that organ hypoperfusion is one of the underlying mechanisms, we might consider SARS-CoV-2 infection as an important trigger for AAC.

To characterize SARS-CoV-2-related cholecystitis, we conducted a literature search using the PubMed database. We came across 17 cases, including our case, reporting AAC related to the infection of SARS-CoV-2 (Table 1) [8–20]. There were 11 men and six women in the series, and the median patient age was 67 years (range: 40–86 years). At least five of the 17 patients had no comorbidities. Regarding the onset of AAC, whereas AAC developed during the treatment for pneumonia (median time lag, 14 days; range, 9–49 days) or was diagnosed at the same time as pneumonia in 15 out of 17 patients, there were two patients (#5 and #6) who had AAC followed by pneumonia. In case #5, AAC developed during treatment for pyelonephritis, and Lap-C was performed following antibiotic therapy. After extubation, the patient developed respiratory failure, was found to be positive for SARS-CoV-2 infection, and died of multiple organ failure on postoperative day five. At the time of diagnosis of cholecystitis, laboratory, or imaging findings suggestive of clotting disorder were confirmed in seven cases. Bruni et al. reported histopathological findings of gangrenous cholecystitis following pneumonia due to SARS-CoV-2, which showed vasculitis possibly caused by SARS-CoV-2-related coagulopathy [11]. In contrast, no pathological findings consistent with vasculitis were found in our case. This suggests that when the degree of ischemia that can trigger acalculous cholecystitis is mild, pathological findings of vasculitis may improve during the waiting period before surgery.

The optimal management of AAC remains controversial, particularly when it is caused by SARS-CoV-2 infection. We classified the severity of SARS-CoV-2-related AAC cases according to the Tokyo guidelines 2018 [6]. Two of the 17 cases were classified as Grade I (mild AAC) and 14 were classified as Grade II (moderate AAC) (Table 1). As for the initial treatment for cases with moderate AAC, emergency cholecystectomy was performed in six patients and PTGBD in four patients. Treatment with PTGBD failed in two patients with gangrenous cholecystitis (#5 and #11), and cholecystectomy was eventually performed 3 days after PTGBD. In case #15, the patient was diagnosed with gangrenous cholecystitis. However, her general condition deteriorated rapidly, and she died of pneumonia, after failing to receive aggressive treatment for AAC. These results suggest that even with AAC caused by SARS-CoV-2, emergency cholecystectomy should be considered according to the Tokyo guidelines 2018 in cases with marked local inflammation. On the other hand, considering that there were cases in which SARS-CoV-2-related pneumonia became evident after surgery, the treatment strategy for AAC with the elevation of inflammatory markers but without marked local inflammation such as gangrenous cholecystitis should be selected cautiously. It is suggested that the infectious virus can be shed for more than 2 weeks after the onset in patients with SARS-CoV-2 who required mechanical ventilation; therefore, elective cholecystectomy followed by sufficient observation may be a safe treatment option for those cases. In such cases, PTGBD could be a useful bridging treatment option.

In conclusion, we have presented a case of AAC related to SARS-CoV-2 pneumonia and conducted a literature review to gain insight into its clinical features. Although the pathophysiology in patients with SARS-CoV-2 has yet to be fully clarified, the SARS-CoV-2 infection might be considered as an important trigger for AAC. This report will help physicians select appropriate therapeutic options for similar situations.

Sources of funding

There is no financial support to declare associated with this study.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Registration of research studies

N/A.

Guarantor

Hana Futagami.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRedit authorship contribution statement

Hana Futagami: writing the paper.
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Declaration of competing interest

None.

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