Case report

Acute acalculous cholecystitis as an early manifestation of COVID-19: case report and literature review

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Abstract. *Background:* The novel coronavirus disease 2019 (COVID-19) has rapidly spread worldwide since the outbreak in Wuhan, China, in 2019, becoming a major threat to public health. The most common symptoms are fever, dry cough, shortness of breath, but subjects with COVID-19 may also manifest gastrointestinal symptoms, and in a few cases an involvement of the gallbladder has been observed. *Case report:* Here we present a case of 50-year-old male with SARS-CoV-2 infection who had abdominal pain, vomiting and diarrhea without respiratory symptoms and was finally diagnosed as acute acalculous cholecystitis (AAC). Laparoscopic cholecystectomy was performed and found a gangrenous gallbladder; the real-time reverse transcription polymerase chain reaction SARS-CoV-2 nucleic acid assay of the bile was negative. We also made a review of the literature and try to understand the hypothetic role of SARS-CoV-2 in the pathogenesis of AAC. *Conclusions*: We highlighted that it is noteworthy to look at gastrointestinal symptoms in patients with SARS-CoV-2 infection and take into account AAC as a possible complication of COVID-19. Although more evidence is needed to better elucidate the role of the pathogenic mechanisms of the SARS-CoV-2 in AAC, it is conceivable that the hepatobiliary system could be a potential target of SARS-CoV-2. (www.actabiomedica.it)

Key words: Coronavirus disease 2019, acute acalculous cholecystitis, laparoscopic cholecystectomy

Introduction

The coronavirus disease 2019 (COVID-19), due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide in few months after the initial outbreak in China, causing a sudden and substantial increase in hospitalizations. The disease can show varied clinical features, ranging from asymptomatic to acute respiratory distress syndrome (ARDS). The most common symptoms are fever, dry cough, shortness of breath and fatigue (1). However, patients can also present with non-classical symptoms, such as gastrointestinal (GI) symptoms. GI symptoms which include loss of appetite, nausea, vomiting, diarrhea and generalized abdominal pain may be at initial presentation of the disease and even in the absence of respiratory symptoms (2). In the context of GI manifestations of COVID 19, an involvement of the gallbladder and biliary tract has been rarely reported. Herein, we describe a case of a male with COVID-19 presenting with GI symptoms, i.e. vomiting, diarrhea and generalized abdominal pain, who was finally diagnosed as acute acalculous cholecystitis (AAC).

Case report

A 50-year-old male patient was admitted to our COVID Medicine Unit on January 03, 2021 with a 6 day history of generalized abdominal pain, low fever, nausea and vomiting, and nasopharyngeal swab polymerase chain reaction (PCR) test positive for SARS-CoV-2 infection. He had preexisting hypertension and type 2 diabetes mellitus for which he was taking medication. He denied any respiratory symptoms (no cough, nor nasal discharge, nor breathing difficulties) and over the last 3 days he has had home medication for pain, i.e paracetamol 1000 mg once per day.

On admission his heart rate was 90 bpm, blood pressure was 130/60 mmHg, body temperature was 36.5°C, respiratory rate was 18 breath/minute and oxygen saturation measured by pulse oximetry was 97 % on room air. He was dehydrated, chest examination was unremarkable, while abdominal examination showed a soft abdomen with moderate tenderness on the right upper quadrant and in the epigastrium and positive Murphy's sign. Blood tests revealed mild elevated C-Reactive-Protein (2.5 mg/dL; n.v. 0.5-1), Lactate Dehydrogenase (300 UI/L; n.v.< 250), procalcitonin (1.55 ng/ml; n.v. < 0.5), d-dimer (1300 ng/ml) values, increased levels of creatinine (2.0 mg/dl; n.v. < 1.5) and urea (110 mg/dl; n.v. <50). Alanin aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin levels and white blood cells were all within the normal range. Antibodies anti Cytomegalovirus and Epstein–Barr virus were negative. Chest X-ray showed very mild interstitial lung disease, while ultrasonography revealed increased thickening of the gallbladder and biliary sludge; no gallstones were identified and the intra- and extrahepatic bile ducts were normal. An AAC was supposed and antibiotic treatment with piperacillin/tazobactam was started. On day 3 of hospitalization, because of presentation of vomiting and nausea and persistent abdominal pain, an abdomen Computed Tomography (CT) scan was performed that ruled out severe gallbladder distension, marked gallbladder wall thickening, and pericholecystic fluid; the liver showed normal size with diffuse increase in echotexture suggestive of mild fatty infiltration; no gallstones, nor bile ducts dilatation were observed (Figure. 1).

The CT scan confirmed the initial suspected diagnosis of AAC and, based on the CT images and the patient symptoms, after discussion on the therapeutic choices with the general surgery team unit, a laparoscopic cholecystectomy was planned and performed.

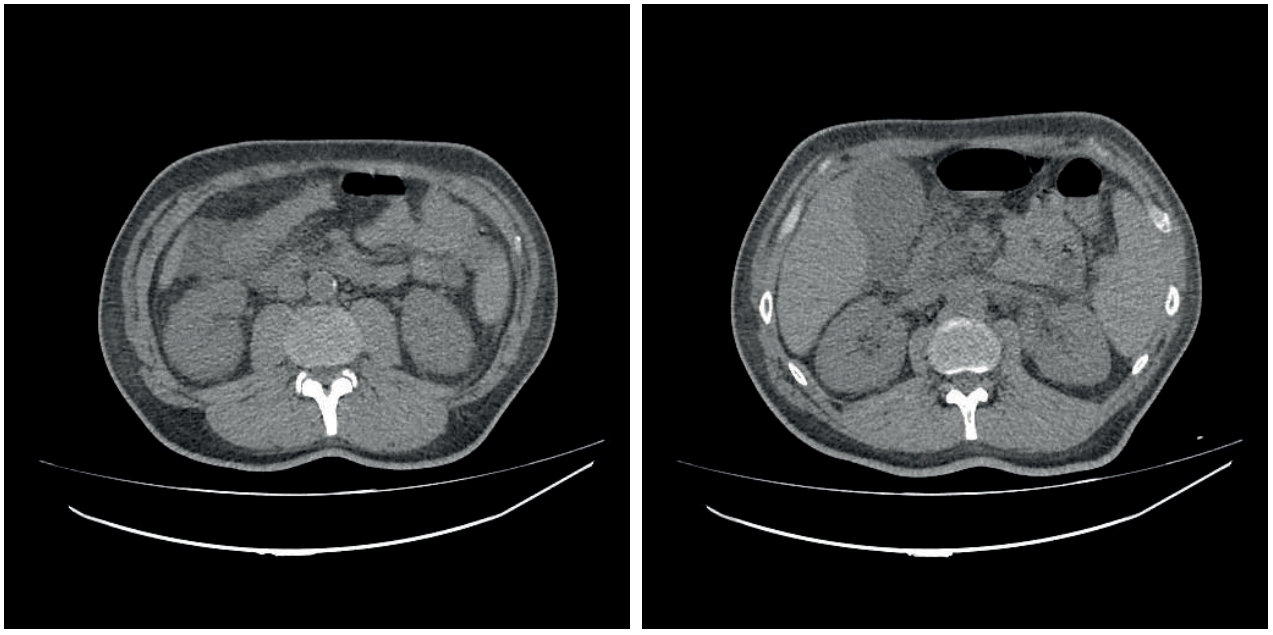

Figure 1. Computed Tomography images

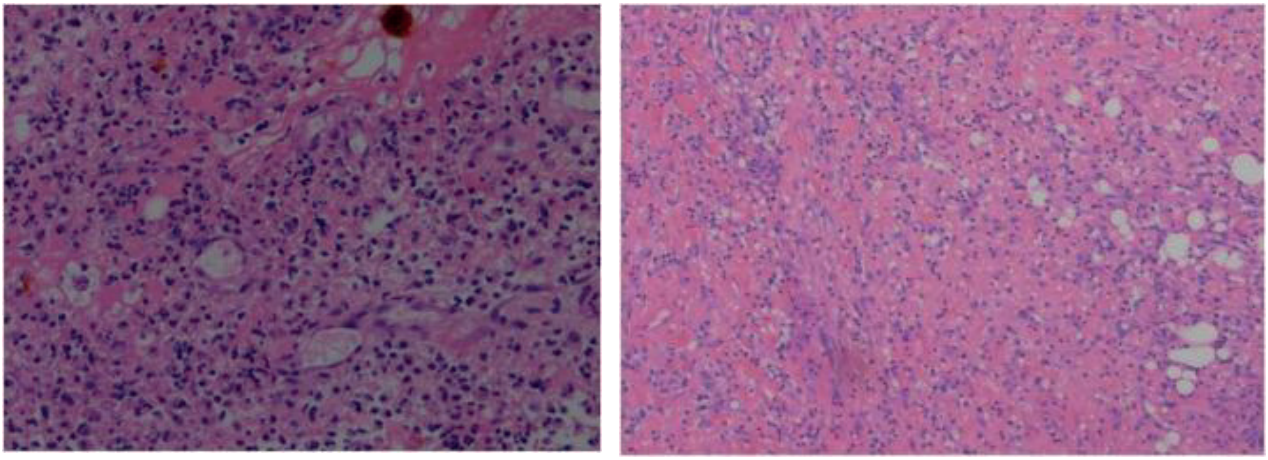

Figure 2. 40x view of hematoxylin and eosin stained sections showing a dense mixed inflammatory infiltrate rich in lymphocytes and neutrophils, edema and hemorrhagic areas of the gallbladder wall.

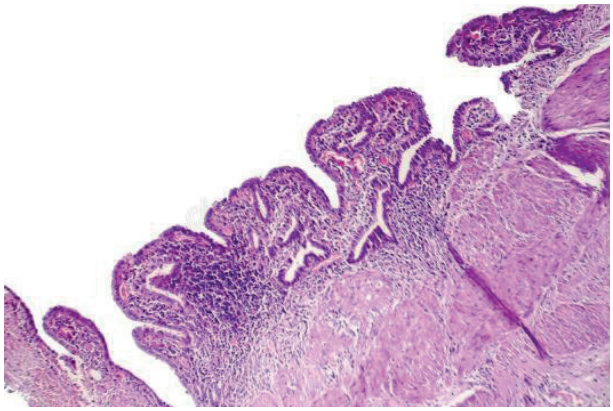

Figure 3. 100x view of hematoxylin and eosin stained section showing gallbladder wall with low-grade inflammation, fibrosis and thickening and hypertrophy of the muscularis propria.

A relaxed and gangrenous gallbladder with perihepatic fluid was intraoperatively found. Gallbladder was sent to the anatomic pathology laboratory for histological examination (Figure. 2-3) and swab for SARS-CoV-2 detection was performed in bile resulting however negative.

After surgery, antibiotic therapy with meropenem was going on. During the postoperative course, on the 4th day after surgery, he showed slight desaturation without subjective dyspnea. A high resolution CT scan of the chest revealed worsening of interstitial pneumonia, showing bilateral hazy ground glass opacities in posterior segments of lower lobes; low flow oxygen through nasal prongs and steroid supplementation was then started. The patient was finally discharged on the 15th postoperative day in satisfactory condition and with SARS-CoV-2 PCR tested as negative.

Discussion

In this report, we described a rare case of gangrenous AAC as a preliminary clinical feature of COVID-19.

Acute acalculous cholecystitis has been already described in subjects with COVID-19 pneumonia, but it has generally been reported in patients with critical illness and who developed acute respiratory distress syndrome and/or were on total parenteral nutrition (TPN). Particularly, Bruni et al. reported acute ischemic gangrenous cholecystitis as a tardive complication in a patient affected by severe SARS-CoV-2 infection that finally required protective invasive mechanical ventilation (3). Similarly, a severe gangrenous cholecystitis with a small perforation of the fundus was identified in a 42-year-old man with severe hypoxemia treated with CPAP (4). In another patient who was intubated because of acute respiratory distress due to COVID-19 pneumonia, a diagnosis of AAC was made at the 49th day of hospitalization, when the patient complained right upper quadrant abdominal pain together with nausea, vomiting and mild corporeal temperature (5). The authors argued that

the acalcolous cholecystitis was related with mechanical ventilation and prolonged TPN, while the gangrenous histopathology pattern was probably caused by severe ARDS of COVID-19 pneumonia that determined vascular insufficiency and gallbladder wall ischemia (5). Accordingly, Wahid et al. described two cases of AAC in patients with prolonged hospitalization for COVID-19 including mechanical ventilation (6), and Scutari et al. presented a case of a woman who required tracheostomy and invasive ventilation and developed AAC after several days of hospitalization (7). In this last case, SARS-CoV-2 RNA was detected in multiple biological fluids, including bile, using "ad hoc" droplet digital PCR assay (7). In another report by Singh et al., a diagnosis of COVID 19 with ARDS was made in a patient on the left ventricular assisted device support that was later complicated by septic shock and AAC with requirement for percutaneous cholecystostomy (8).

Two cases of COVID-19 presenting as AAC were reported by Balaphas A et al; particularly, they were old patients with critical illness; the first one was initially diagnosed as sepsis due to pyelonephritis, and the second patient was on dialysis for end-stage renal disease with type 2 diabetes and hypertension. Only the first patient underwent a laparoscopic cholecystectomy, and histological analysis of the gallbladder did not demonstrate any inflammation, while viral RNA was detected in the gallbladder wall (9). A case of AAC treated with ultrasound-guided percutaneous transhepatic gallbladder drainage was also reported by Ying et al. in a woman presented with fever, chest stuffiness, and diarrhea who developed abdominal pain after 10 days of hospitalization; the PCR test of the bile showed no evidence of virus invasion of the gallbladder (10). Asti et al. managed three patients who developed acute abdomen while recovering from COVID-19 pneumonia and were diagnosed as AAC; emergency laparoscopy confirmed gallbladder gangrene in all. However, the authors did not specify whether the patients presented with GI or respiratory symptoms, developed respiratory distress, and required mechanical ventilation (11).

Another case of AAC was reported by Alhassan et al; they described a 40 years old healthy woman that developed fever, malaise, and right hypochondrial pain after fourteen days of COVID 19 infection and was managed conservatively with broad spectrum antibiotics. The authors stated the possibility that acalculous cholecystitis might result from post COVID dysregulated immune response (12).

In our patient AAC was diagnosed as an early clinical feature of SARS-CoV-2 infection. Initially, radiology imaging detected very mild interstitial pneumonia and the patient did not show any respiratory symptoms; slight desaturation and radiological worsening of interstitial lung disease were shown during the postoperative course. The patient did never develop ARDS and was not on TPN. Furthermore, acalculous cholecystitis got complicated with necrosis as shown intraoperatively and by histological examination.

As above mentioned, AAC is a well-known occurrence in critically ill patients and it is caused by hypomotility of the gallbladder which is responsible of increased intraluminal pressure evolving in inflammation, ischemia and necrosis (13).

At present it is not still clear what is the precise role of SARS-CoV-2 in gallbladder inflammation. It has been demonstrated that SARS-CoV-2 has proteins that bind to the cell receptor angiotensin-converting enzyme 2 (ACE2) that expresses in relatively high amounts in other organs besides the lungs, such as liver and gallbladder, and in vascular endothelium (14,15). Therefore, the virus can invade, multiply, and cause infection in several organ systems. Alternatively, SARS-CoV-2 could infect small intestinal enterocytes which express ACE 2 receptor as well and get to the gallbladder through the bile recirculation process. It can also be supposed that the virus may spread to extrapulmonary organs including the gallbladder and give typical clinical manifestations (16). However, only very few papers reported viral RNA detection in the gallbladder wall or bile of a patient with AAC (7,9).

Moreover, SARS-CoV-2 has been associated with vascular inflammation, and vasoactive mediators can play a role in the pathogenesis of AAC by promoting ischemic gallbladder changes (17). It is possible, as well, that gallbladder wall ischemia occurs because of low-flow state due to fever and dehydration or heart failure, as occurs in acute bacterial and viral illnesses.

It has also to be stated that AAC has been described during other viral illnesses such as human immunodeficiency virus, hepatitis B virus, Cytomegalovirus and Epstein-Barr virus infections (18). Furthermore, coagulation dysfunction has been reported to be associated with COVID-19 that can cause vessel microthrombosis

even in the absence of overt disseminated intravascular coagulation (16), and other factors including bile stasis, systemic inflammation, immunosuppression, opportunistic infections, can contribute to coagulopathy and gallbladder ischemia.

Finally, chronic illnesses such as diabetes, hypertension, atherosclerotic disease have been considered predisposing factors in patients with AAC (18). Since our patient had preexisting hypertension and type 2 diabetes, we have to state that these potential risk factors could be a confounding variable for gallbladder pathogenesis. Moreover, since swab for SARS-CoV-2 detection on biliary fluid was negative, AAC and COVID-19 might have been just synchronous and not causally related; however, the underlying pathogenic mechanisms of SARS-CoV-2 infection, even though they are not fully clarified, suggest that the hepatobiliary system could be a potential target of SARS-CoV-2.

In conclusion, it is noteworthy to look at gastrointestinal symptoms in a patient with SARS-CoV-2 infection and take into account AAC as possible complication of COVID-19, although rare, particularly in those subjects with multiple other diseases or potential risk factors for AAC.

More evidence is needed to better understand the role of the pathogenic effects of the SARS-CoV-2 in AAC.

Conflict of Interest: each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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