

## **Necrotized Acalculous Cholecystitis Associated with SARS-CoV2 (COVID-19)**

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### **Abstract**

**Introduction:** The coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome (SARS-Cov-2), has rapidly become a global pandemic, mainly affecting the respiratory system. However, it has been demonstrated that it also affects other systems such as the digestive, renal, hepatic, integumentary, and circulatory systems, having endothelial injury as a common denominator. Injuries to the digestive system have had a significant impact on the surgical area, as surgeons have had to quickly react to this unprecedented clinical challenge by systematically reusing operating rooms.

Treatment for COVID-19 is symptomatic and oxygen therapy represents the main treatment intervention for patients with severe infections. However, in patients with acute abdomen, treatment has not changed, open or laparoscopic surgery remain as the gold standards, in addition to the specific treatment for COVID-19.

**Objective:** Presentation before the surgical community of a clinical case from the Ticomán General Hospital of Mexico City's Ministry of Health about the presence and association of acalculous cholecystitis associated with COVID-19.

**Results:** Clinical case of a 77-year-old female patient who was admitted to the emergency room due to colicky abdominal pain located in the right hypochondrium and epigastrium, presenting nausea and multiple vomiting episodes of bile, showing data of a systemic inflammatory response, as well as acute abdomen. She was examined by our general surgery department and with an Exploratory Laparotomy the surgical management was decided, which resulted in the following findings: Necrotized acalculous gallbladder in its entirety, multiple adhesions Zühlke IV loop/wall, loop/gallbladder, gallbladder/loop, perivesical fluid of cloudy appearance approximately 300cc. Hepatocystic triangle with distortion of the anatomy, performing a Partial Reconstituting Cholecystectomy. Surgical specimen is sent to pathology where micro cuts are made with hematoxylin and eosin staining and Masson's Trichome staining observing micro thrombosis; she has a torpid evolution during the postoperative period, and presents desaturation up to 80% in the environment, a test is taken for COVID-19, which is positive, triggering a metabolic response and significant respiratory failure of the patient, which results in her death.

**Discussion:** COVID-19 has been shown to replicate primarily in airway epithelial cells via input receptors for angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 can cause liver injury similar to respiratory coronaviruses, since they share the same genome, although their incidence is lower than that of SARS-CoV infection; 5%-37% versus 60-70%, respectively. Histological and immunohis-

tochemical studies in cutaneous, pulmonary, and intestinal pathology involve microvascular injury and thrombosis, which consists in the activation of the alternate pathway and the complement lectin pathway.

Acute acalculous cholecystitis (AAC) is the inflammation of the gallbladder without evidence of calculi inside; uncommon amongst the spectrum of biliary disease. Most patients with acalculous cholecystitis have multiple risk factors such as trauma, cardiopulmonary resuscitation, mechanical ventilation, sepsis, burns, human immunodeficiency virus (HIV), immunodeficiency states, long-term total parenteral nutrition, and major surgery.

The entry of the SARS-CoV-2 virus is mediated by expressed ACE 2 receptors in the liver, gallbladder, and vascular endothelium; therefore, it is possible that COVID-19 causes endotheliitis in the gallbladder, thus leading to inflammation and necrosis. Laparoscopic cholecystectomy remains the treatment of choice for acute cholecystitis even in the COVID-19 era.

**Conclusion:** COVID-19 infection leads to systemic inflammation and endothelial damage to various organs, with acalculous cholecystitis being one of the variants of this disease, which may potentially complicate the clinical status of these patients. Currently, there is no clear consensus to treat acalculous cholecystitis secondary to COVID-19, but it depends mainly on the clinical status of the patient and the severity of the disease.

In conclusion, acalculous cholecystitis secondary to COVID-19 infection can have fatal complications such as necrosis and perforation of the gallbladder; Laparoscopic surgery is no more likely to spread COVID-19 infection than open surgery.

**Keywords:** Cholecystitis; Acalculous; COVID-19; SARS CoV2; Acute Abdomen; Necrosis

### Introduction

An outbreak of cases with inexplicable lower respiratory infections detected in Wuhan, China was first reported in December 31<sup>st</sup>, 2019. Since the causal agent could not be identified, it was called "pneumonia of unknown etiology". Currently the etiology is attributed to a new virus which belongs to the coronavirus (CoV) family. On January 11, 2020 it was announced that this disease was caused by Coronavirus (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-Cov-2), which subsequently spread worldwide.

SARS-CoV-2 can cause liver injury similar to respiratory coronaviruses, since they share the same genome, although their incidence is lower than that of SARS-CoV infection; 5% - 37% versus 60 - 70%, respectively. SARS-CoV-2 infects the epithelial cells of the gastrointestinal glands of the stomach, duodenum, and rectum, and, to a much lesser extent, the esophagus, for which reason gastrointestinal symptoms, such as diarrhea, vomiting, and abdominal pain have been reported during the course of the disease.

Acute acalculous cholecystitis (AAC) is the inflammation of the gallbladder without evidence of calculi inside; uncommon amongst the spectrum of biliary disease. The pathogenesis is related to gallbladder stasis due to lack of gallbladder stimulation. This condition favors secondary bacterial proliferation, with *E. coli* being the most frequent. And if not treated promptly, it can lead to gallbladder ischemia, tissue necrosis, and perforation, leading to sepsis and multiple organ failure.

Ultrasound is the conclusive imaging study, with 85% sensitivity and 95% specificity. Two major criteria or one major and two minor criteria must be met to demonstrate acute acalculous cholecystitis.

If acalculous cholecystitis is complicated by sepsis, necrosis, or perforation, surgical intervention is necessary, either a percutaneous cholecystostomy or an open or laparoscopic cholecystectomy. Laparoscopic cholecystectomy remains the treatment of choice for acute cholecystitis even in the COVID-19 era.

## Objective of the Study

Presentation before the surgical community of a clinical case from the Ticomán General Hospital of Mexico City's Ministry of Health about the presence and association of acalculous cholecystitis associated with COVID-19.

## Case Report

This is a 77-year-old female patient who was admitted to the emergency department on November 14 due to colicky abdominal pain located in the mesogastrium and right hypochondrium with 8/10 intensity, accompanied by nausea and vomiting of gastrobile content on multiple occasions, and non-quantified fever, self-medication with magaldrate and paracetamol on 2 occasions, with a partial improvement of symptoms, and subsequent increase in symptoms, for which she attended this unit. Control laboratory tests were taken upon admission with the following report: Leukocytes  $14.5 \times 10^3/\text{ml}$ , Neutrophils 89.3%, Lymphocytes 6.4%, Hemoglobin 16.9 gr/dl, Hematocrit 50.3%, Platelets  $215 \times 10^3/\text{ml}$ , Glucose 180 mg/dl, Creatinine 3.02 mg/dl, Alkaline Phosphatase 153 IU/L, ALT 193 IU/L, AST 179 IU/L, GGT 305 IU/L, TB 2.10 mg/dl, DB 1.0 mg/dl, IB 1.10 mg/dl. Likewise, a General Urine test was performed, with the following report: Color Orange, Cloudy Appearance, pH 5.5, Negative Nitrites, Negative Ketone Bodies, Leukocytes 8 - 10 x field, Erythrocytes 18-20 x field, Moderate Cells, Amorphous Urate Crystals, Moderate Bacteria, Granular Cylinders, Mucin ++.

Arterial blood gases test: pH 7.35,  $p\text{CO}_2$  31mmHg,  $p\text{O}_2$  129 mmHg,  $\text{HCO}_3$  17.1 mmol/L, BE -7.4 mmol/L,  $\text{SO}_2$  94%.

Chest X-ray: An increased bronchoalveolar structure is observed, with flow cephalization, as well as bilateral perihilar infiltrates (Figure 1).



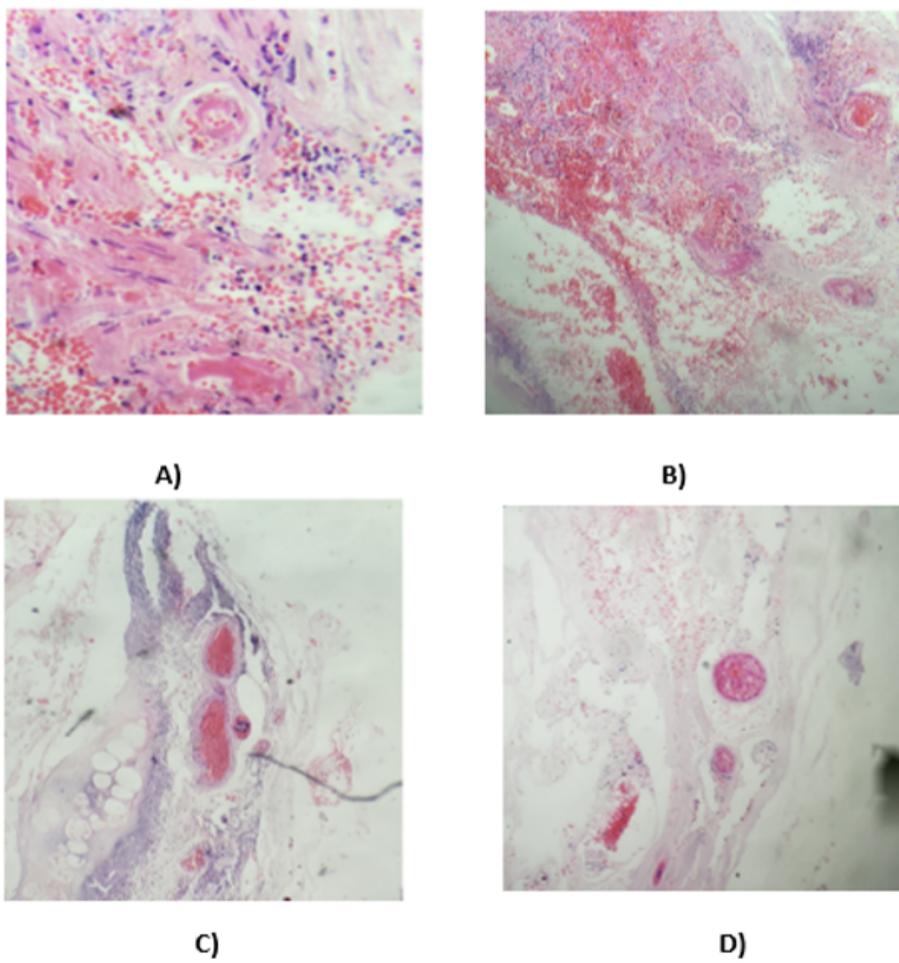
**Figure 1:** Chest X-ray upon admission to the emergency department, where a discrete widening of the mediastinum, and bilateral perihilar infiltrate are observed, as well as a slight recess of the costodiaphragmatic sinuses.

Abdominal ultrasound: Gallbladder with a 5mm thick wall, no visualization of images inside, 6mm thick common bile duct, no visualization of images inside. Kidneys with ultrasound changes in relation to probable urinary tract infection. No collections in abdominal spaces, highly distended intestinal loops and slight edema on its walls, as well as decreased peristalsis.

She is conscious and oriented to people, time and space, with adequate integument color, poor hydration status, neck without adenomegaly, on auscultation, chest show pulmonary fields with the presence of bilateral interscapular-vertebral rales, precordium shows rhythmic heart sounds, without added sounds, distended abdomen as a result of adipose panniculus, positive Murphy sign, normoactive peristalsis, with acute abdomen data, for which surgical management was decided on November 14, and an exploratory laparotomy was performed with the following findings: Gallbladder size 10x6cm, fully necrotized (Figure 2), no calculus inside, multiple Zühlke IV adhesions loop/wall, loop/gallbladder, gallbladder/loop, perivesical fluid with a cloudy appearance approximately 300cc. Hepatocystic triangle with anatomy distortion. Therefore, a Partial Reconstituting Cholecystectomy is performed, a surgical piece is sent to the pathology area where micro cuts with Hematoxylin and eosin staining are made, and Masson's Trichome staining, which shows microthrombosis, with focal ischemic changes (Figure 3).

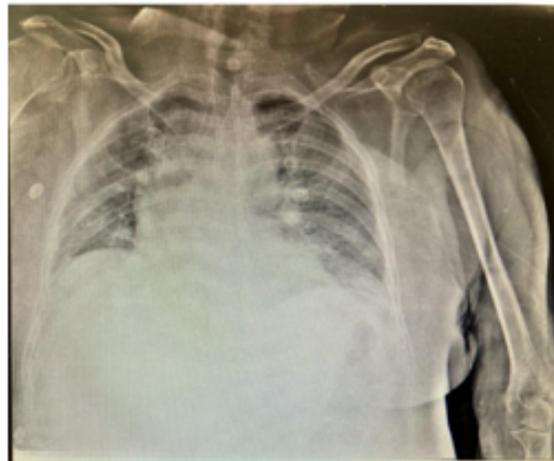


**Figure 2:** Intraoperatively, a fully necrotized gallbladder is visualized.



**Figure 3:** Micro sections with H&E staining which shows micro thrombi. (a and b), micro sections with Masson's Trichome stain, and micro thrombi are observed (c and d). Images taken from the pathology department of the Ticomán General Hospital.

After the surgery, she had a torpid evolution, with a fever of 38°C, as well as dyspnea on small and medium exertion, saturation up to 80% of room air, tachycardia, oliguria, a new control chest x-ray was taken, which shows a generalized opacity in both pulmonary fields, as well as an increase in the bronchoalveolar weft (Figure 4). In this situation, the TRMC-19 Questionnaire is performed with a score of 48 points, being classified as high risk; then the polymerase chain reaction test of reverse transcriptase (RT-PCR) is taken, and it is positive, for which the diagnosis of SARS-Cov 2 (COVID-19) was confirmed. Patient shows significant deterioration in respiratory and metabolic function, and blood gas test is taken which reports the following pH: 7.22, pCO<sub>2</sub> 20mmHg, pO<sub>2</sub> 105 mmHg, HCO<sub>3</sub> 8.2 mmol/L, BE -19.5 mmol/L, SO<sub>2</sub> 85%, death took place on November 18.



**Figure 4:** Chest x-ray on the 2nd postoperative day, with an increase in the vascular pattern and bilateral perihilar infiltrates. The patient already has a COVID-19 diagnosis.

### Discussion

An outbreak of cases with inexplicable lower respiratory infections detected in Wuhan, China was first reported in December 31<sup>st</sup>, 2019 [1]. Since the causal agent could not be identified, it was called “pneumonia of unknown etiology”. Currently the etiology is attributed to a new virus which belongs to the coronavirus (CoV) family. On January 11, 2020 it was announced that this disease was caused by Coronavirus (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-Cov-2), which subsequently spread worldwide [2].

Initially called 2019-nCoV, experts from the International Committee on the Taxonomy of Viruses (ICVT) called it the SARS-CoV-2 virus, because it is similar to the virus that caused the SARS outbreak (SARS-CoV) [2].

COVID-19 is round or elliptical and often pleomorphic, with a diameter of approximately 60-140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, disinfectant containing chlorine, peroxyacetic acid, and chloroform, except chlorhexidine [3].

COVID-19 has been shown to replicate primarily in airway epithelial cells via input receptors for angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 can cause liver injury similar to respiratory coronaviruses, since they share the same genome [4], although their incidence is lower than that of SARSCoV infection; 5% - 37% against 60 - 70% respectively [5,6]. Histological and immunohistochemical studies in cutaneous, pulmonary, and intestinal pathology involve microvascular injury and thrombosis, which consists in the activation of the alternate pathway and the complement lectin pathway [7].

SARS-CoV-2 infects the epithelial cells of the gastrointestinal glands in the stomach, duodenum, and rectum, and, to a much lesser extent, the esophagus [8]. So gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain have been reported during the course of the disease. SARS-CoV-2 RNA was detected in patients' stools by reverse transcriptase polymerase chain reaction (RT-PCR) on day 7 of the disease.

Acalculous cholecystitis was first described by Duncan in 1844 and is seen more frequently in critically ill ICU patients due to hypokinesia or dysfunctional emptying of the gallbladder [9].

Acute acalculous cholecystitis (AAC) is the inflammation of the gallbladder without evidence of calculi inside, uncommon amongst the spectrum of biliary disease [10]. Most patients with acalculous cholecystitis have multiple risk factors such as trauma, cardiopulmonary resuscitation, mechanical ventilation, sepsis, burns, human immunodeficiency virus (HIV), immunodeficiency states, long-term total parenteral nutrition, and major surgery [11].

The pathogenesis is related to gallbladder stasis due to lack of gallbladder stimulation. This condition favors secondary bacterial proliferation, and the most frequent bacteria are: *E. coli*, *Klebsiella*, *Bacteroides*, *Proteus*, *Pseudomonas* and *Enterococcus faecalis*. And if not treated promptly, it can lead to gallbladder ischemia, tissue necrosis and perforation, leading to sepsis and multiple organ failure [9].

The mechanism of injury due to the cytokine-mediated inflammatory response is not well understood. However, this response is known to cause increased vascular permeability, multiple organ failure, and death, with persistent elevation of cytokines such as IL-6, IL-8, and TNF alpha [10]. Furthermore, post-COVID 19 cytokine release syndrome has been described in association with a possible antibody complex-mediated reaction that can cause systemic inflammation and may be a rationale for acute acalculous cholecystitis [11,12]. Entry of the SARS-CoV-2 virus is mediated by expressed ACE 2 receptors in the liver, gallbladder and vascular endothelium; therefore, it is possible that COVID-19 can cause endotheliitis in the gallbladder, causing inflammation and necrosis [13,14].

Clinical data can be diverse, and the most prominent are: pain in the right hypochondrium and right upper quadrant or epigastrium, fever, abdominal distention, absence or decrease of peristaltic sounds, nausea, vomiting and anorexia. Positive Murphy sign can be found during the examination.

Ultrasound is the conclusive imaging study, with 85% sensitivity and 95% specificity. Two major criteria or one major and two minor criteria must be met to demonstrate acute acalculous cholecystitis. Among the major criteria are: gallbladder wall greater than or equal to 4mm thick, perivesical fluid, distention greater than 5 cm in length, intramural gas, or emphysematous cholecystitis. The minor criteria are: bile sludge, distention greater than or equal to 8 cm in length or greater than 5 cm in width, simple abdominal computed tomography (CT) or magnetic resonance imaging (MRI) is recommended if the resource is immediately available [15,16].

If acalculous cholecystitis is complicated by sepsis, necrosis, or perforation, surgical intervention is necessary, either a percutaneous cholecystostomy or an open or laparoscopic cholecystectomy [17]. Laparoscopic cholecystectomy remains the treatment of choice for acute cholecystitis even in the COVID-19 era. All current guidelines recommend laparoscopic surgery as the gold standard, due to the better results in terms of mortality, morbidity, and postoperative hospital stay compared to open cholecystectomy [18-20].

However, although SARS-Cov-2 RNA has recently been detected in the peritoneal cavity, there is no evidence to indicate the presence of SARS-CoV-2 in surgical smoke [21]. No evidence has emerged to suggest that the risk of COVID-19 infection related to laparoscopic surgery may be greater than that of open surgery, either for the patient or for healthcare professionals. Therefore, it is not considered that patients should be denied the benefits that high-quality studies have shown as being related to minimally invasive surgery. We recommend that surgeons take the necessary safety measures to reduce the risk of viral spread in the operating room and to ensure that patients continue to benefit from the advantages of laparoscopic surgery [22].

### Conclusion

COVID 19 infection leads to systemic inflammation and endothelial damage to various organs, with acalculous cholecystitis being one of the variants of this disease, which can complicate the clinical status of these patients. Currently, there is no clear consensus to treat acalculous cholecystitis secondary to COVID-19, but it depends mainly on the clinical status of the patient and the severity of the disease. Some patients can be treated conservatively, while in other cases in which this initial measure is not enough, they may require surgical intervention. In conclusion, acalculous cholecystitis secondary to COVID-19 infection can have fatal complications such as necrosis and perforation of the gallbladder, which leads the patient to a state of sepsis that can even lead to death; therefore, this entity should not be underestimated and it should be treated in a timely manner.

We also conclude that laparoscopic surgery is not more likely to spread COVID-19 infection than open surgery, so its use should not be restricted, measures should be taken to be organized in such a way that it is safely performed, even in the current situation, to guarantee the patient the best results that minimally invasive surgery has already shown.

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