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# A rare complication in a Covid-19 positive patient with sigmoid colon cancer-hemoperitoneum due to gallbladder necrosis following micro-thrombosis

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## ABSTRACT



Covid-19, also known as acute respiratory syndrome 2019-nCoV, severe acute respiratory syndrome (SARS) 2, and Wuhan pneumonia, is a viral respiratory disease caused by a SARS-associated coronavirus (SARS-CoV-2). The most serious complications of Covid-19 are due to the development of micro-thrombosis in various organs and systems as a result of the high levels of pro-inflammatory cytokines (tumor necrosis factor alpha, interleukin 1 and 6) which initiate the activation of coagulation and the generation of thrombin. Several studies demonstrated the poor outcome of Covid-19-infected patients who underwent surgery, suggesting that surgery may accelerate and exacerbate Covid-19 progression. We report the case of an 81-year-old patient admitted as an emergency with Covid-19 pneumonia, hemoperitoneum, ischemic acute cholecystitis and obstructive sigmoid cancer. Cholecystectomy, pneumoperitoneal lavage, and Hartmann operation were performed under combined epidural-spinal anesthesia. This technique has some advantages compared to spinal and epidural techniques, such as: rapid onset of analgesia and the possibility of obtaining the desired sensory level, control of the anesthetic block, and ensuring postoperative analgesia. The unfavorable outcome of this case is due to the occurrence of the cytokine storm and coagulation disorders, with the change in the related biological constants, both from a biochemical and systemic point of view.

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## Introduction

Covid-19, also known as acute respiratory syndrome 2019-nCoV, severe acute respiratory syndrome (SARS) 2, and Wuhan pneumonia, is a viral respiratory disease caused by a SARS-associated coronavirus (SARS-CoV-2) [1,2]. The primary mode of infection is through droplets of respiratory secretions from infected people, which are expelled by sneezing, coughing, or exhaling [3,4]. The virus has an incubation period of 2 to 14 days, with an average of 3 days, although cases with an incubation period of up to 24 days have been reported [5,6]. The disease may initially be asymptomatic or with few symptoms, and patients may later develop fever, cough, shortness of breath, muscle pain, and fatigue, followed by pneumonia, acute respiratory distress syndrome, and death [7].

The major complications in patients diagnosed with COVID-19 are: pneumonia, hypoxemic respiratory failure/acute respiratory distress syndrome (ARDS), diffuse alveolar lesions, secondary bacterial infections, sepsis and septic shock, liver dysfunction, multi-organ dysfunction (MSO), and gastrointestinal bleeding [8,9]. The most serious complications of Covid-19 are due to the development of micro-thrombosis in various organs and systems due to the increased level of pro-inflammatory cytokines (tumor necrosis factor alpha, interleukin 1 and 6) which initiate the activation of coagulation and the generation of thrombin [10]. Several studies have demonstrated the poor outcome of Covid-19-infected patients who underwent surgery, suggesting that surgery may accelerate and exacerbate the progression of COVID-19 disease [11,12].

## Case Presentation

We present the case of an 81-year-old male patient, with a personal medical history of hypertension, upper digestive hemorrhage, gastroesophageal reflux disease, bulbar angiodysplasia, colon diverticulosis, colon polyps, hepatic steatosis, who was admitted to the Gastroenterology Clinic with diffuse abdominal pain, hematemesis, with a “coffee ground” vomitus, and multiple diarrheal stools.

The laboratory tests performed upon hospital admission revealed a biological inflammatory syndrome (leukocytosis 12,000, PCR-43 mg/l), chronic renal failure (urea-80 mg/dl, creatinine 2.01 mg/dl), RT-PCR negative for SARS CoV-2 infection. The abdominal ultrasound revealed that the liver had a homogeneous, hyperechoic echostructure, the right lobe having 12.5 cm, and a cyst of approx. 1.8 cm in the left lobe. The pancreas, the spleen, the gallbladder, the main bile ducts in normal relations, the portal vein and both kidneys of normal size and appearance.

Colonoscopy showed normal rectal mucosa, sigmoid colon with diverticula, and a polyp of about 2 cm with long pedicle at approximately 20 cm from the anal orifice. At approximately 25 cm from the anal orifice, the lumen was obstructed by a tumor mass (Figure 1) with polypoid appearance that bled slightly when touched, and which did not allow the passage of the endoscope. These colonoscopy findings indicated the need for surgical consultation, but the patient refused both the referral and the surgical intervention, for which reason he was discharged at his own risk.



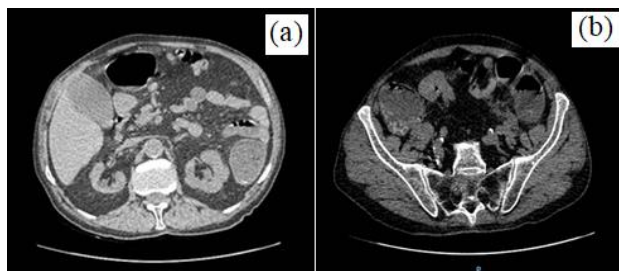
**Figure 1.** Colonoscopy view of the sigmoid tumor

Three weeks later, the patient presented to the Emergency Unit with exacerbation of the abdominal pain, abdominal flatulence, abolished gas and stool transit, and altered general condition, for which reason he was readmitted to the Gastroenterology Clinic. The laboratory tests performed in the emergency unit reveal leukocytosis of 20,000, hemoglobin 10 mg/dl, PCR-300 mg/dl, urea-200

mg/dl, creatinine 2.70 mg/dl, D-Dimer-4620 ng/ml, and a negative PCR test for Covid-19.

During the hospital stay, the patient presented dyspnea, cough and a febrile syndrome. The chest CT revealed a lung tissue condensation process and bilateral pulmonary emphysema. When the Covid-19 diagnostic test was repeated, it returned positive. An infectious disease consultation was requested. The patient was transferred to the infectious disease clinic and a treatment with Kaletra (an antiviral drug for systemic use), Clexane 0.4 ml injection (an anticoagulant), Plaquenil (hydroxychloroquine), dexamethasone, analgesics, and antispasmodics was initiated.

The patient presented an altered general condition, with the accentuation of the abdominal complaints, and therefore an abdominal CT-scan was performed (Figure 2). It showed a left pericardial condensation process with positive air bronchogram, hepatorenal cysts, right renal atrophy, hiatal hernia, enlarged gallbladder, wall thickening of the descending colon.



**Figure 2.** Abdominal CT scan: (a) hepatorenal cysts, right atrophic kidney, enlarged gallbladder (b) descending colon with a thickened wall

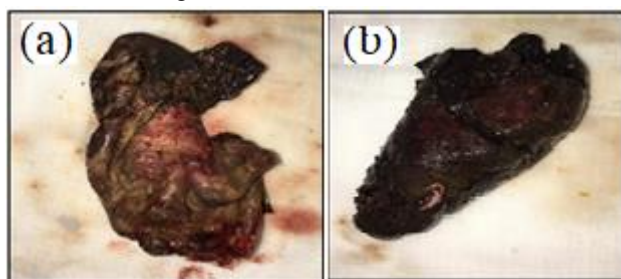
A surgical consultation was requested again. Upon the clinical examination, the patient had an altered general condition, cold, cyanotic skin, he was unstable hemodynamically and with abnormal breathing pattern, enlarged abdomen, rebound tenderness on abdominal palpation, marked meteorism on percussion, abolition of gas and stool transit, digital rectal examination revealed no changes except no stool at this level. Based on the clinical and laboratory investigations, the diagnosis of acute surgical abdomen and intestinal obstruction was made and emergency surgery was indicated. The informed consent was obtained after the reasonable disclosure of the risks and therapeutic alternatives were discussed [13].

After a brief preoperative preparation, the patient was transferred directly to the operating room and underwent surgery under combined spinal-epidural anesthesia (CSE). This type of anesthesia has the advantage of avoiding orotracheal intubation, which involves the mobilization of aerosols infected with SARS Cov2, and has adverse postoperative respiratory outcomes.

This type of anesthesia consists of performing a spinal anesthesia in the intervertebral space L2-L3, using 2ml (10 mg) of 0.5% hyperbaric bupivacaine, combined with 25 µg

Fentanyl and mounting an epidural catheter in the intervertebral space T7-T8, being used in addition to anesthesia and analgesia, but which can also be used postoperatively with a role in analgesia and the early resumption of the bowel movement.

Intraoperatively, when opening the peritoneal cavity, a large amount of hemoperitoneum was found, with blood and bilious appearance, which was evacuated. There was also a large hematoma below the liver, which enclosed the gallbladder with its perforation, without other changes in the liver. The evacuation of the hematoma and antegrade cholecystectomy were performed. The surgical specimen was sent to the laboratory for the histopathological examination (Figure 3).



**Figure 3.** a) Gangrenous gallbladder; b) Necrosis and coagulated blood inside the gallbladder

At the level of the sigmoid colon, a stenotic tumor mass was found (see Figure 4), which invaded the ileum and its mesentery and a suprastenotic dilatation of the colon up to the cecal level was found. A meticulous viscerolysis was performed with the dissection of the tumor adhesions to the surrounding ileum and mesentery.

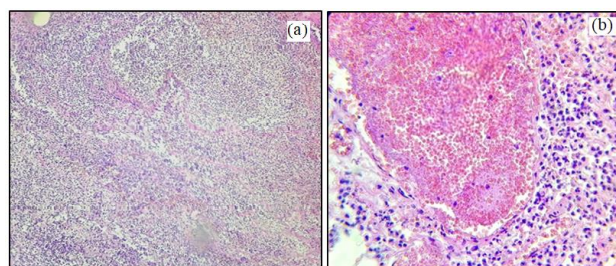


**Figure 4.** Stenotic sigmoid colon tumor

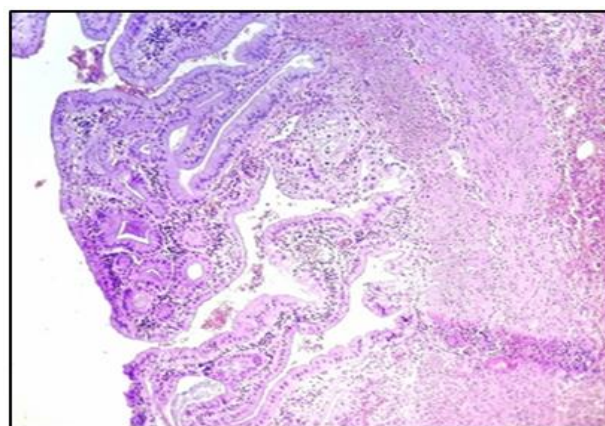
The Hartman operation was performed with the closure of the sigmoid loop with a TA stapler and iliac anus on the descending colon, with the histopathological examination of the surgical specimen. At the end of surgery, massive washing, drainage in the Douglas and sub-hepatic space, parietorrhaphy in the anatomical layers, separate threads on the skin and sterile dressing were performed.

Intraoperatively, towards the end of surgery, the patient presented an episode of acute pulmonary edema which improved after the administration of Furosemide, CPAP mask over the face mask, and Dobutamine. In the intensive care unit, the patient presented severe bradypnea with decreased oxygen saturation and severe bradycardia, with a slow unfavorable course. Prolonged hospitalization in the intensive care unit led to pressure sores, which were managed with antibiotics and essential oils, effective against the several microorganisms, such as *Bacillus subtilis*, *Clostridium perfringens*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enteritis*, *Candida albicans* and *Saccharomyces cerevisiae* [14].

The histopathological examination described a gallbladder wall with modified architecture, a parietal area with extensive necrosis that included all the layers, with the presence of multiple extensive hemorrhagic areas and an intense inflammatory infiltrate, predominantly with polymorphonuclear cells. The muscularis layer was slightly hypertrophied and the subserosal layer presented extensive areas of necrosis (Figure 5a), with cellular detritus and the presence of a rich polymorphonuclear inflammatory infiltrate, marked vascular congestion present in the remaining wall with vascular lumina loaded with hematoma conglomerates (Figure 5b).



**Figure 5.** The histopathological examination of the gallbladder: a) Necrotic mucosa; b) Congested vessel



**Figure 6.** Tissue fragment sent separately for the histopathological examination showing the appearance of organized hematoma, consisting of erythrocyte and leukocyte conglomerates, without the presence of cellular atypia.

## Discussions

The acute complications of sigmoid cancer are represented by intestinal obstruction or intestinal perforation accompanied by peritonitis, abscesses or hemorrhages, but also by the occurrence of secondary outcomes; therefore, the diagnosis must be made and the surgical treatment must be performed as soon as possible. When stenotic complications require emergency surgery, colocolic anastomosis is not recommended due to the high risk of anastomotic leakage. Authors report average leak rates ranging from 1 to 3% for ileocolic anastomoses and up to 10–20% for low colorectal anastomoses, being one of the most frequent causes of all 30-day mortality and a cause of long-term morbidity including poor bowel function, reduced quality of life (QoL), increased risk of cancer recurrence, and high rates of a permanent stoma [15-17].

The SARS-COV- 2 superinfection is a major factor in a cancer patient who initially refused the surgical treatment and, as a result, presents respiratory and cardiac decompensation, thus making the surgical process even more difficult. In the reported case, the choice of the type of anesthesia was one of the key points in the performance of the surgical procedure and postoperative outcome of the patient. General anesthesia and laparoscopy, by insufflating CO<sub>2</sub> to create the pneumoperitoneum, determine cardiovascular and respiratory imbalances which can generate respiratory acidosis, hypercapnia, with heart rhythm disorders and acute myocardial ischemia in people with pre-existing cardiovascular or lung conditions [18,19]. The combined CSE technique offers certain advantages, compared to spinal and epidural techniques, e.g.: the rapid onset of analgesia and the possibility of obtaining the desired sensory level, control of the anesthetic block, and providing postoperative analgesia.

This type of anesthesia consists in performing a spinal anesthesia in the intervertebral space L2-L3 using 2 mL (10 mg) of 0.5% hyperbaric bupivacaine, combined with 25 µg Fentanyl and mounting an epidural catheter in the intervertebral space T7-T8, and it is used to complete the anesthesia and analgesia, but it can also be used postoperatively with a role in analgesia and the early resumption of the intestinal transit [20]. The risks of the technique are: post-puncture headache, migration of the catheter into the subarachnoid space, and transient paresthesia caused by the spinal needle [21]. Careful perioperative care of the vascular, hemodynamic and respiratory status should be provided in order to prevent these adverse events in the elderly [20], especially in cases with acute pulmonary pathology, such as SARS-Cov-2 infection.

In approximately 10% of the cases, digestive manifestations may occur due to the binding of SARS-Cov-2 at the level of ACE receptors in the intestinal tract, causing fever, abdominal pain, nausea, vomiting, transit

disorders, and thus it has to be included in the differential diagnosis in case of emergency surgeries in order to avoid medical errors [22,23]. The mechanisms of abdominal pain may be ischemic or non-ischemic. The thrombotic mechanism involves the endothelial damage clinically manifested as mesenteric vessel ischemia, renal vessel infarcts, omental infarcts, and ischemic cholecystitis.

According to recent studies, SARS-CoV-2 is associated with prothrombotic changes which are the main factors of arterial and venous thromboembolism, along with elevated D-Dimer levels [24-26]. COVID-19, associated with the production of pro-inflammatory cytokines, mediates the activation of mononuclear and endothelial cells and tissue factor resulting in the activation of coagulation and the generation of thrombosis [20-22]. Endothelial cell dysfunction mediated by COVID-19 infection results in increased thrombin production with decreased fibrinolysis resulting in hyper-coagulopathy [27-29]. Hypoxia, specific to patients with COVID-19, can cause thrombosis by increasing blood viscosity and activating the transcription factor associated with hypoxia, resulting in an increase in D-dimer, fibrin/fibrinogen degradation products, and elevated blood fibrinogen levels, especially in the patients with chronic diseases [30,31].

On February 16th, 2020, Liu and his team at the Tongji Medical College, Wuhan, performed the first autopsy on the body of an 85-year-old patient infected with Covid-19, revealing not only lung, brain, liver, and kidney damage, but also of other tissues due to the occurrence of necrosis at these levels [32].

Almost at the same time, Xu et al, at PLA General Hospital, Beijing, performed a minimally invasive autopsy on a 50-year-old patient whose death was caused by severe SARS-CoV-2 infection [33]. Microvesicular steatosis and a slight hepatic and portal insufficiency were found at the hepatic level, having the infection with SARS - CoV-2 as a possible cause. Following the autopsy, the occurrence of inflammatory infiltrates in the examined tissues was demonstrated, without other substantial lesions [33,34].

The autopsy on 38 Indian COVID-19 patients showed that 33 patients had fibrin thrombi in their arterial vessels and elevated D-Dimer level in their blood [35], and the autopsies on 3 Chinese patients revealed cell damage and necrosis with thrombosis of large and small vessels in the heart, kidneys, liver, gallbladder, and intestines [34,36]. In the US, the autopsy on 5 patients showed that the capillaries of the lungs, liver, and brain were obstructed by thrombosis-associated vasculopathy, and the microvascular injury was observed [37].

According to a study performed on 16 COVID-positive corpses, aged between 70 to 90 years, mostly male, having hypertension, diabetes, and chronic ischemic heart disease as comorbidities, and D-Dimer levels ranging from 5,000

to 4000 mc/L, 7 patients had necrosis of the hepatic tissue and 9 patients had portal lymphocytic infiltrate with thrombosis in the central lobular vein [37].

## Highlights

- ✓ SARS-Cov2 infection in an oncological patient changes the therapeutic approach not only in terms of anesthesia, but also of surgery, due to the resulting intraoperative and postoperative complications.
- ✓ The confirmation by histopathological examination of the existence of micro-thrombi in the gallbladder vasculature, with necrosis and its perforation, supports the recent studies that mention the occurrence of coagulation disorders in Covid-19-positive patients.

## Conclusions

SARS-Cov2 infection in an oncological patient changes the therapeutic approach not only in terms of anesthesia, but also of surgery, due to the resulting intraoperative and postoperative complications.

The confirmation of the existence of microthrombi in the gallbladder vasculature by histopathological examination, with necrosis and perforation, supports the recent studies that mention the occurrence of coagulation disorders in Covid-19-positive patients.

Gallbladder necrosis is an extremely rare complication of Covid-19 disease, and therefore, it must be publicized, in order to warn any doctor treating this disease about the existence of this complication.

The choice of combined spinal-epidural anesthesia, combined with analgesia-sedation, provided good intraoperative comfort and maintained cardiac and respiratory parameters within a normal range. The inflammatory cascade together with the coagulation disorders affect not only the lungs, but also other organs such as the liver, bowels, kidneys and brain, data confirmed by the autopsies performed on SARS - CoV - 2 infected corpses. The unfavorable outcome of the reported case was due to the cytokine storm with the change of the involved biological constants, and severe fluid-coagulant imbalance.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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