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Case Report

Post COVID 19 acute acalculous cholecystitis raising the possibility of underlying dysregulated immune response, a case report

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ABSTRACT

Introduction: Novel Coronavirus disease 2019 or COVID-19 has rapidly spread throughout the world and has become an unprecedented pandemic. It has a vast spectrum of clinical presentations and can affect various organs. Rarely, it has been reported to cause acalculous cholecystitis in a non ICU setting patient.

Case presentation: Here we report a rare association of COVID 19 with acalculous cholecystitis in a 40 years old healthy woman. She developed fever, malaise, generalized body weakness, and right hypochondrial pain after fourteen days of COVID 19 infection, raising the possibility of Post COVID dysregulated immune response resulting in acalculous cholecystitis. She was managed conservatively with broad spectrum antibiotics.

Discussion: Acalculous cholecystitis primarily occurs due to the gall bladder's hypomotility and most commonly seen in critically ill patients such as severe burns, mechanically ventilated patients, and prolonged parenteral nutrition. The management depends upon treating the underlying pathology and, in some severe cases, may need surgical intervention as well. Up to our knowledge, COVID 19, causing acalculous cholecystitis, is a rare association described only in a few critically ill patients but not in young, healthy patients. It can be attributed to the body's dysregulated immunological response against the virus resulting in systemic inflammation.

Conclusion: Currently, there is are no clear guidelines for managing acute cholecystitis in COVID-19 patients. It depends on the patient's clinical state and disease severity. We aim to highlight the importance of early diagnosis and management in such clinical scenarios to avoid fatal complications.

1. Introduction

Coronavirus disease 2019 or COVID 19 due to SARS-COV-2 started in Wuhan city of China in December 2019 as a cluster of unknown pneumonia cases [1]. It rapidly spread throughout the world and was declared a pandemic on March 11, 2020 [2]. Patients usually develop fever, cough, flu-like symptoms, and may further progress to cause pneumonia and life-threatening acute respiratory distress syndrome (ARDS) [3]. Non-specific symptoms, such as diarrhea, vomiting, abdominal pain, are also seen in COVID 19 patients [3]. We describe a case of COVID 19 pneumonia leading to acalculous cholecystitis in a young, healthy female who presented to the hospital with high-grade fever, myalgia, and right hypochondriac pain. Acalculous cholecystitis was first described by Duncan in 1844 and is more commonly seen in critically ill ICU patients due to hypokinesis or dysfunctional gall bladder emptying [4]. The surgical team was consulted, and the patient was managed with IV fluids and antibiotics. The patient did not require any invasive procedure and remained stable throughout the hospital course and follow up. The possibility of systemic inflammation response syndrome due to dysregulated immunity against the virus might be the reason. Timely diagnosis with prompt management can avoid fatal complications like gall bladder ischemia, perforation and even death. This article has been reported in accordance with SCARCE guidelines 2018 [5].

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Abbreviations

COVID 19	Coronavirus disease 2019
Rrt-PCR	real time reverse transcriptase polymerase chain reaction
CRP	C - reactive protein
ALT	alanine transaminase
AST	aspartate transaminase
PCR	Polymerase chain reaction
ANC	absolute neutrophil count
ICU	intensive care unit
IV	intravenous
WBC	white blood cells
US:	ultra sound
CT	computed tomography
IL:	interleukins
TNF	Tumor necrosis factor
LVAD	left ventricle assisted device
ARDS	acute respiratory distress syndrome
HIV	human immunodeficiency virus
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2. Case presentation

A 40-year-old young, healthy woman presented to the emergency department by ambulance with a two-day history of high-grade fever, generalized body aches, nausea, and a moderate right hypochondrium pain. There was no previous history of any chronic disease, medications, allergy or psychological illness. Her family history was remarkable hypertension in father. She was diagnosed with COVID 19 fourteen days ago. Initial vitals showed a high-grade fever of 39.5C, blood pressure of 97/70mmhg, increased heart rate of 118/min, and normal respiratory rate. There was mild tenderness on the right hypochondrium and a positive Murphy's sign. There was no jaundice or scratch marks on the body. Based on the history and physical examination, differential diagnosis of acute cholecystitis, acute hepatitis and liver abscess were made. Therefore, keeping in mind the targeted approach to the presentation further investigations were performed. Blood investigations were remarkable for high white cell count, increase neutrophils, and elevated inflammatory markers, specifically *C*-reactive protein (CRP), D-dimers, ferritin, and interleukins as shown in Table 1.

A Chest XR was performed to look for any new pneumonic consolidation as a possible source of infection. The patient had a history of COVID 19, and Chest XR showed bilateral lower lung patchy pulmonary consolidations and left-sided-pleural effusion, as shown in Fig. 1.

Due to the history of right hypochondrial pain, tenderness, and suspected differential diagnosis, an abdomen ultrasound was performed. Abdominal ultrasound revealed thickened gall bladder wall, surrounding pericholecystic fluid, and minimal free fluid in the abdomen and the pelvis. These findings were consistent with acute acalculous cholecystitis, as shown in Fig. 2.

Sepsis workup including blood cultures and urine cultures was unremarkable. Surgical team was consulted and the patient was commenced on broad spectrum antibiotics with IV Piperacillin Tazobactum 4.5 gm three times daily and azithromycin 500mg daily with watchful waiting. The patient became hypotensive and was resuscitated with IV fluids under ICU care but did not require mechanical intubation. Repeat COVID real-time reverse transcriptase (Rrt-PCR) came out inconclusive. After resuscitation, the patient became normotensive but continued to spike high-grade fever. Therefore a CT abdomen was performed to rule out any intra-abdominal collection as a source of infection. Lower image slides of the CT abdomen revealed bilateral pleural effusion with consolidation, ground-glass opacities in the right middle lobe with atelectasis correlating with COVID-19 aetiology. And no intra-abdominal collection found as shown in Fig. 3.

Her antibiotics were changed to IV meropenem 500mg BID and fever was settled. On the 9th day of her hospital course, the patient became more stable with the trending down of inflammatory markers as mentioned in table: 1. another repeat COVID-19 Rrt-PCR was performed and turned out to be negative. She was discharged and further followed up on outpatient basis by the surgical team via telemedicine for one-month post-discharge. The patient was asked about symptoms of abdominal pain and its associated characters like localization, intensity, nature, associated features to pain like food or empty stomach, and fever spikes during the follow-up. Furthermore, she did not report any of the symptoms. She remained stable throughout her follow up period.

3. Discussion

Acalculous cholecystitis is an acute necroinflammatory disease of the gallbladder and is considered a severe illness with high morbidity and mortality. The reported mortality is from 30 to 50% depending upon the clinical state of the patient [4]. The majority of patients with acalculous cholecystitis have multiple risk factors such as trauma, cardiopulmonary resuscitation, mechanical ventilation, sepsis, burns, human immunodeficiency virus (HIV), immunocompromised states, prolonged total parenteral nutrition, and major surgery [4,6]. The pathogenesis is related to gall bladder stasis secondary to lack of gall bladder stimulation resulting in bile concentration and building up of intra-luminal

Table 1
Laboratory parameters of the patient.

Lab parameters	Normal values	Patient values at presentation	Day 9
White blood cells ($x10^3/\mu L$)	4.0–10.0	17.8	9.0
Lymphocyte ($x10^3/\mu L$)	1.0–3.0	1.3	1.5
Absolute neutrophil count ($x10^3/\mu L$)	2.0–7.0	14.9	6.6
platelet count ($x10^3/\mu L$)	150–400	529	350
Alkaline phosphatase (U/L)	35–104	102	60
ALT (U/L)	0–33	102	31
AST (U/L)	0–32	55	28
D-dimer (mg/L FEU)	0.00–0.44	5.39	–
Lactic acid (mmol/L)	0.5–2.2	0.8	–
Ferritin (ug/L)	12.0–240	348 μg/L	–
Interleukin −6 (pg/mL)	≤7 pg/mL	416 pg/mL	–
Procalcitonin (ng/ml)	<0.5	0.53 ng/mL	0.01
CRP(mg/L)	0–5	394.1	90

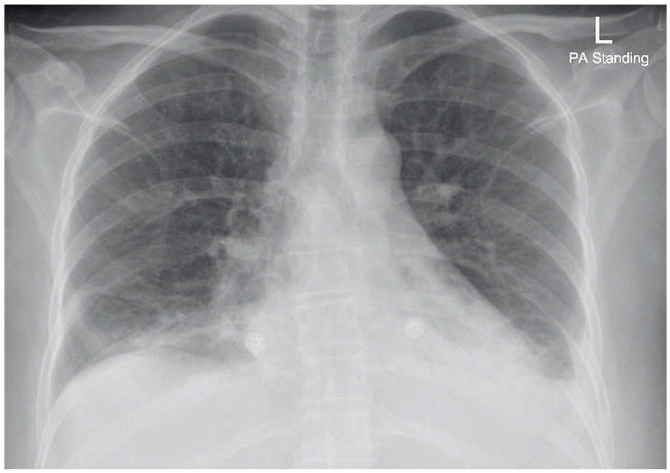

Fig. 1. Chest XR showing bilateral lung consolidations and left sided obliteration of costophrenic angle.

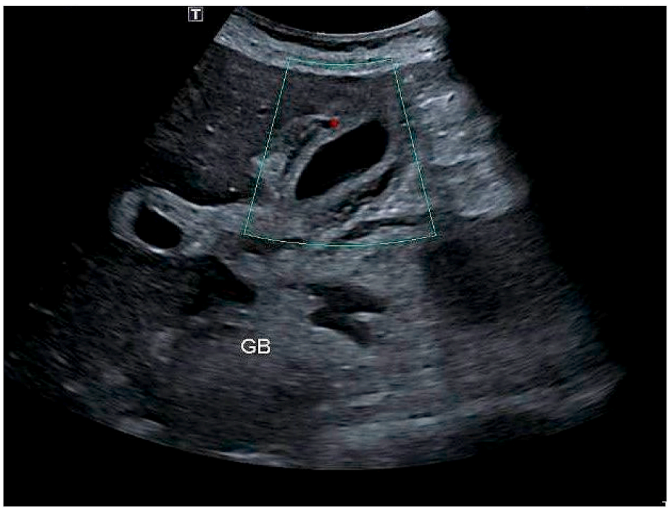

Fig. 2. US gall bladder showing pericholecystic fluid and edema around the gall bladder.

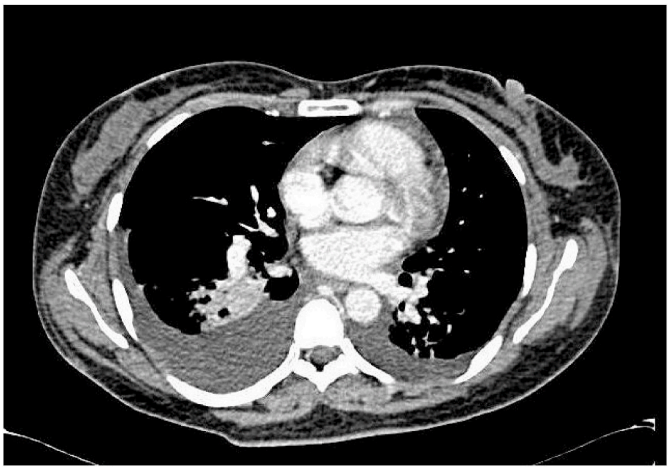

Fig. 3. CT scan abdomen: bilateral pleural effusion, more on the left side and with bilateral ground glass shadows.

pressure in the organ. Furthermore, the static condition invites secondary bacterial infections, predominantly *Escherichia coli*, Klebsiella, Bacteroides, Proteus, Pseudomonas, and *Enterococcus faecalis* [4]. And if not addressed promptly, it can lead to gall bladder ischemia, tissue necrosis, and fatal perforation, causing sepsis and multi-organ failure [4].

Recently a case report has described acalculous cholecystitis in a COVID 19 patient that was critically ill and was on mechanical ventilation [6]. The possibility of acalculous cholecystitis, in this case, could be related to severe illness, mechanical ventilation, and prolonged parenteral nutrition. However, another plausible mechanism could be due to acute cytokine release syndrome which is also seen in COVID 19 patients and studied by Croteau et al. in patients with relapsing-remitting multiple sclerosis during or shortly after alemtuzumab treatment [6,7]. The mechanism of injury in cytokine storm is poorly understood. It is assumed to cause increase vascular permeability, multi organ failure and fatality with persistently raised cytokines like IL-6, IL-8 and TNF alpha [8]. Moreover, post COVID 19 cytokine release syndrome has been described in association with possible antibody complex mediated reaction that can cause systemic inflammation and can be a rationale of acute acalculous cholecystitis as seen in our case [8]. SARS-CoV-2 virus entry is mediated by angiotensin-converting enzyme (ACE) 2 receptors expressed in the liver, gall bladder, and vascular endothelium; therefore, it is also possible that the COVID 19 might have caused endothelitis in the gallbladder leading to inflammation and necrosis [9,10]. In another case described by Singh and colleagues, COVID-19 was diagnosed in a patient on the left ventricular assisted device (LVAD), which was complicated with ARDS and developed septic shock secondary to acalculous cholecystitis [11]. However, most of the described cases in the literature were critically ill and developed acute respiratory distress syndrome, but in our case, the patient was diagnosed with mild COVID-19 pneumonia and, after fourteen days, developed acute onset of right-sided hypochondrial pain with fever and myalgias. She was not intubated nor had any chronic medical illness. She was immediately started on IV fluids and broad-spectrum antibiotics with good response and remained stable throughout her hospital stay. If acalculous cholecystitis gets complicated with sepsis, necrosis or perforation, then further surgical intervention with percutaneous cholecystostomy or cholecystectomy may be required [9–11]. But in our case, early diagnosis and conservative medical management with broad spectrum antibiotics yielded good outcome. This signifies the importance of timely management in stable patients that can prevent further clinical deterioration and surgical intervention. Other viral infections such as HIV and hepatitis B have been associated with acalculous cholecystitis but only a few numbers of cases have been described in the literature in association with COVID-19 [11].

4. Conclusion

COVID 19 infection leads to systemic inflammation, and acalculous cholecystitis may complicate such patients' clinical status. We want to highlight the importance of early diagnosis and prompt management of acalculous cholecystitis in COVID 19 patients through our case by a conservative approach to treat the underlying cause and possible administration of broad-spectrum antibiotics and IV fluids. Currently, there are no clear guidelines to treat acalculous cholecystitis in COVID 19 pandemic but mainly depends upon the patient clinical status and disease severity. Some may require surgical intervention as well in unresponsive, critically ill patients. In conclusion, acalculous cholecystitis in COVID19 infection can have fatal complications like gall bladder necrosis and perforation, leading to sepsis and even death; therefore, it should not be missed and managed in a timely manner.

5. Consent of the patient

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

The case has been approved by the medical research council of the institute for publication with a specified designated number. Ethical approval is not required for case presentation as per our institutional policies.

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Author contribution

Study concept or design – Shahda Mohamed Alhassan, Phool Iqbal.

Data collection – Shahda Mohamed Alhassan, Phool Iqbal.

Data interpretation – Shahda Mohamed Alhassan, Phool Iqbal, Muhammad Sohaib Qamar.

Literature review – Shahda Mohamed Alhassan, Phool Iqbal, Lubna Fikrey, Mohanad Ibrahim Mohamed Ibrahim, Muhammad Sohaib

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Drafting of the paper – Shahda Mohamed Alhassan, Phool Iqbal, Lubna Fikrey, Mohanad Ibrahim Mohamed Ibrahim, Muhammad Sohaib Qamar.

Editing of the paper – Shahda Mohamed Alhassan, Phool Iqbal, Masautso Chaponda, Waqar Munir.

Registration of research studies

Not required for case report.

Guarantor

Dr. Shahda Mohamed Alhassan.
Dr. Phool Iqbal.
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Declaration of competing interset

None of the authors had any personal or financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2020.11.031.

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