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ORIGINAL

Liver abscesses in patients with coronavirus infection

Abscesos hepáticos en pacientes con infección por coronavirus

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Abstract

Background: Recent studies demonstrate that COVID-19 is associated with systemic infectious and inflammatory diseases. Various symptoms of liver and gastrointestinal damage are often diagnosed in patients with COVID-19 but there is limited data on liver abscesses.
Material and methods: The current analysis includes 11 patients who were treated at Botkin Hospital, Moscow in the period from September 2021 to May 2022 for liver abscesses and who previously suffered from COVID-19 infection.
Results: Surgical intervention has been performed in the volume of transcutaneous drainage of liver abscesses under ultrasound guidance. The complex therapy included antibacterial drugs (according to the results of a microbiological study with the determination of the sensitivity of the flora to antibacterial drugs), anti-inflammatory drugs, daily sanitation of the abscess cavity based on the proposed algorithm. Seven patients (63.6%) were discharged with drainage under the supervision of clinic doctors. Four patients (36.4%), who had significant regression of the abscess cavity had their drainage removed before discharge.
Conclusion: Patients with prior COVID-19 may develop liver abscesses. It is important to carry out thorough diagnostic evaluation in patients who complain of fever and/or abdominal pain after coronavirus infection and timely drainage of these abscesses. The current study demonstrates that percutaneous drainage, sanitation of the cavity combined with empirical antibiotic treatment is the optimal treatment modality for this group of patients.

Keywords: coronavirus infection; liver abscess; percutaneous drainage.

Resumen

Antecedentes. Estudios recientes demuestran que la COVID-19 está asociada a enfermedades infecciosas e inflamatorias sistémicas. En pacientes con COVID-19 suelen diagnosticarse diversos síntomas de daño hepático y gastrointestinal, pero existen pocos datos sobre abscesos hepáticos.
Material y métodos. El presente análisis incluye 11 pacientes que fueron tratados en el Hospital Botkin, Moscú, en el período comprendido entre septiembre de 2021 y mayo de 2022 por abscesos hepáticos y que previamente sufrieron infección por COVID-19.
Resultados. La intervención quirúrgica se ha realizado en el volumen de drenaje transcutáneo de abscesos hepáticos bajo guía ecográfica. La terapia compleja incluyó fármacos antibacterianos (de acuerdo con los resultados de un estudio microbiológico con la determinación de la sensibilidad de la flora a los fármacos antibacterianos), fármacos antiinflamatorios, saneamiento diario de la cavidad del absceso basado en el algoritmo propuesto. Siete pacientes (63,6%) fueron dados de alta con drenaje bajo la supervisión de médicos clínicos. A cuatro pacientes (36,4%), que presentaron una regresión significativa de la cavidad del absceso, se les retiró el drenaje antes del alta.
Conclusiones. Los pacientes con COVID-19 previa pueden desarrollar abscesos hepáticos. Es importante realizar una evaluación diagnóstica exhaustiva en los pacientes que se quejan de fiebre y/o dolor abdominal tras una infección por coronavirus y drenar a tiempo estos abscesos. El presente estudio demuestra que el drenaje percutáneo, el saneamiento de la cavidad combinado con un tratamiento antibiótico empírico es la modalidad de tratamiento óptima para este grupo de pacientes.

Palabras clave: infección por coronavirus; absceso hepático; drenaje percutáneo.

Introduction

The coronavirus infection (COVID-19) is an acute infection of the respiratory system, caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV2) that has become a public health problem worldwide[1]. COVID-19 has causes significant global morbidity, mortality but also disruption to society and economies. However, the true incidence of COVID-19 is likely to have been underestimated, mostly due to individuals underreporting mild symptoms or inadequate testing strategies[2]. SARS-CoV2 belongs to the Coronaviridae family and is a single-stranded RNA virus. The main target of this virus is the angiotensin-converting enzyme 2 (ACE2) receptor. Therefore, it was initially considered that COVID-19 primarily affects the respiratory system[3].

In addition, ACE2 receptors are also present in the liver, gastrointestinal tract, heart, kidneys, pancreas, muscles, and nervous system. Therefore, the true nature of post-COVID-19 effects and changes in the body are yet to be discovered. According to recent data, COVID-19 is regarded as a systemic infectious and inflammatory disease[4,5].

There have been several studies of liver disease in patients who have had SARS-CoV2 infection. Elevated transaminases are seen in more than 50% of patients and are an indicator of liver damage and overall severity of the disease[6]. Studies have shown that coronavirus can bind to ACE2 receptors on cholangiocytes and lead to their dysfunction, which causes systemic inflammatory response and liver damage[7]. In addition, immune-mediated inflammation in severe forms of COVID-19 is accompanied by an increase in the level of C-reactive peptide (CRP), D-dimer, interleukin-6 and ferritin, which altogether contribute to liver damage[8].

Pyogenic liver abscess is an emerging healthcare problem with an increasing incidence worldwide[9,10]. The true incidence of this disease varies between countries and is hard to assess. The main reasons are increase in frequency of hepatobiliary interventions and organisms with multidrug resistance and comorbidities [9-11]. However, liver abscesses after COVID-19 infection is a new challenge. Some of the manifestations of infectious diseases may mask liver abscesses and therefore are a diagnostic challenge for physicians in patients with SARS-CoV2. Moreover, they may superimpose on already severe condition of the patient leading to increased morbidity and mortality.

Epidemiological studies have shown that half of the patients had impaired liver function, in particular an increase in the level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), and 1% of patients had severe liver damage, including liver abscess [12]. Nevertheless, there is limited data on liver dysfunction and infection in patients with COVID-19. We present an analysis of a group of patients who previously suffered from COVID-19 and developed liver abscesses during their recovery period.

Materials and methods

The work is based on the analysis of 11 patients who were treated at the surgical clinic of Botkin hospital from September 2021 to May 2022 for liver abscesses. The diagnosis of liver abscess was based on medical records, clinical picture, imaging studies, laboratory results, cytological and microbiological results. The study had a prospective design. The complete inpatient and outpatient medical records were extracted to collect the following clinical variables: age, sex, previous data on COVID-19 infection, BMI, comorbidities. The main characteristics of patients are presented in **table I**. The criteria of inclusion in the study were previous history of coronavirus infection (positive PCR test for SARS-CoV2) with previous vaccination. All patients underwent a systematic comprehensive preoperative examination and postoperative control. All patients underwent laboratory tests (white blood cell count, AST level, ALT, CRP, SARS-CoV2 IgM and IgG antibodies), abdominal ultrasound (USG), abdominal computer tomography (CT) with intravenous contrast, abdominal magnetic resonance imaging (MRI) with intravenous contrast, cytological and microbiological studies. Liver abscess was defined as a hepatic lesion on imagining (USG, CT, MRI) in patients with corresponding clinical picture, presence of pus in the aspirate, positive culture, response to antibiotic treatment and drainage. Percutaneous drainage was performed under local anesthesia (2% lidocaine solution) with USG guidance by two healthcare professionals ("free hand" technique): a surgeon and medical ultrasonography specialist. Aspirated pus was sent for gram stain and culture. The acquired quantitative variables were expressed as mean (M) with standard deviation (SD).

Results

Eleven patients with complaints of abdominal pain and hyperthermia were admitted to the surgical clinic of Botkin hospital. During ultrasound examination of the abdominal cavity, all patients had volumetric liquid formations in the liver (from 1 to 3), ranging in size from 20x18x14 mm to 185x150x135 mm. All patients showed changes in the laboratory values, namely leukocytosis, increased ALT, AST and CRP (**Tables I, II**).

All hospitalized patients had a history of coronavirus infection 4-6 months before the present hospitalization, without prior vaccination. Six patients (54.5%) had

Table I: Major clinical characteristics of the patients.

Parameters		
Age (M ± SD, min-max), years	61.2 ± 9.3 (38-74)	
Sex, n (%)	Males 6 (54.55%)	Females 5 (45.45%)
BMI (M ± SD, min-max), kg/m^2	27.8 ± 2.9 (21.9-32.4)	
SARS-CoV-2 antibodies (M ± SD, min-max)	IgM 0.93 ± 1.03 (0.19-4.01)	IgG 163.17 ± 130.7 (7.96-358.17)

Table II: Laboratory values.

Parameters	Before	After
Leukocytes (M ± SD, min-max), 10^9/l	16.1 ± 4.19 (8.4-24.1)	7.7 ± 1.3 (5.6-13.6)
ALT (M ± SD, min-max), U/l	93.1 ± 56.8 (17.3-363)	19.9 ± 7.4 (5-30.1)
AST (M ± SD, min-max), U/l	90.3 ± 65.2 (21-282)	25.4 ± 8.6 (14-41)
CRP (M ± SD, min-max), mg/l	248.6 ± 41.6 (177.8-333.8)	103.8 ± 40.7 (3-175.2)

bilateral polysegmental pneumonia during the period of COVID-19 disease. In the remaining 5 patients (44.5%) there was no evidence of pneumonia. These patients underwent a blood test for antibodies to SARS-CoV-2 (IgM and IgG). All patients showed a significant increase in IgG antibody titer (**Table I**).

Further examination with CT of the abdominal cavity with intravenous contrast, in these patients, reveled multi-chamber hypodense formations in the liver parenchyma, uneven fuzzy contours, actively accumulating contrast agent along the periphery (**Figure 1**).

Figure 1: Multispiral CT. Liver abscess (arrow). A. Frontal section. B. Axial section. Multiloculated hypodens mass in the liver parenchyma with uneven fuzzy contours (arrow).

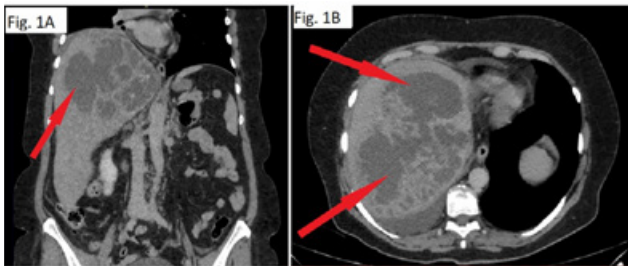
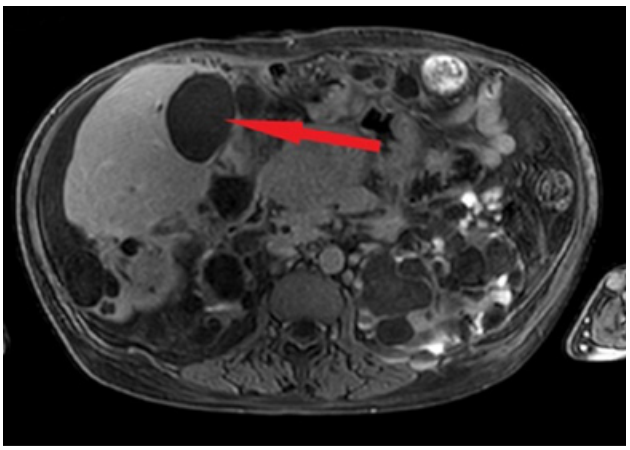


Figure 2: Magnetic resonance imaging. Liver abscess (arrow). Axial section.



Moreover, these patients underwent MRI of the abdominal cavity with intravenous contrast, in which the above formations are described as cystic, with signs of limited diffusion and sedimentation, poorly accumulating the contrast drug in its wall (**Figure 2**).

Blood test for antibodies to parasitic liver diseases (Echinococcus) and tumor markers (AFP) were negative in all cases.

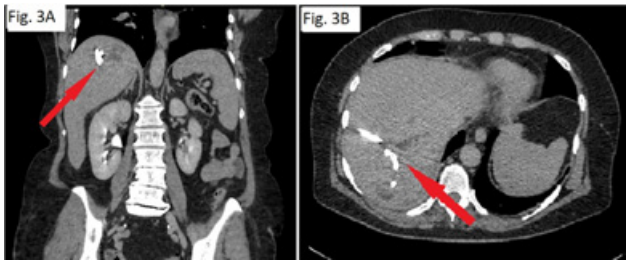
After a comprehensive examination, all patients underwent percutaneous drainage of liver abscess under ultrasound guidance. Thick creamy pus was obtained in all cases. The contents of the abscess cavity were subjected to cytological and microbiological studies. In all of the cytological studies there were half-decayed neutrophilic leukocytes in large numbers and macrophages. Microbiological analysis revealed Klebsiella pneumonia in all patients in various titers and additionally, in 2 cases Escherichia coli. The sensitivity of the obtained microflora to antibacterial drugs was determined in order to guide the treatment process, however none of the patients required change of their initial regiment. The analysis of antibiotic resistance pattern demonstrated that Klebsiella pneumonia was sensible in all cases to amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam, gentamicin, amikacin, imipenem, ertapenem, meropenem, levofloxacin, ciprofloxacin, trimethoprim/sulfamethoxazole, cefazolin, cefepime, ceftazidime, ceftriaxone, ceftolosan/tazobactam, cefuroxime and vancomycin. It was resistant to ampicillin and fosfomycin in all cases.

All patients underwent complex treatment, including appropriate antibacterial therapy based on the results of microbiological resistance, anti-inflammatory therapy, daily sanitation of abscess cavities with antiseptic solutions. All patients received i/v antibiotic treatment (cefoperazone with sulbactam 2 g every 12 hours). The medium duration of treatment was 12 days (minimum 8 days and maximum 18 days). There was an improvement in the general condition, regression of fever, a significant decrease in the flow rate of discharge through the drainage, and in some cases, its complete absence.

During control laboratory studies, normalization of all indicators was noted, including leukocytes, transaminases and CRP. The dynamics of laboratory parameters is shown in **table II**.

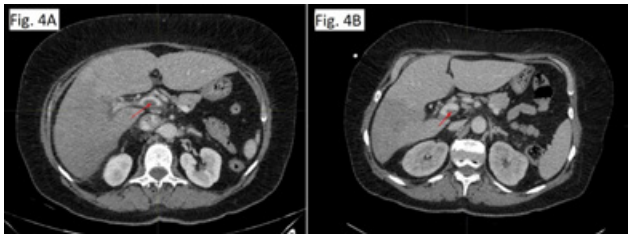
During control instrumental studies (including fistulography), there was a significant decrease in abscess cavities, and in 4 cases, complete regression of the cavity till the size of the drainage tube (**Figure 3**). There was no communication with the bile ducts in any cases.

Figure 3: Multispiral CT. Liver abscess after drainage. A. Frontal section. B. Axial section. The drainage tube can visualized (arrow) and the abscess cavity has decreased after therapy.



In one case (9.09%) the patient had thrombosis of the portal vein, which gradually resolved after treatment. Six patients had comorbid conditions. Two patients had diabetes mellitus type 2 (18.18%), two patients had end stage chronic kidney disease (18.18%) and another 2 had endophthalmitits (18.18%).

Figure 4: Multispiral CT. A. Portal vein thrombus (arrow). B. Decrease of the portal vein thrombus after 11 days of treatment (arrow).



All patients were discharged to the outpatient follow-up stage in a stable satisfactory condition. Seven patients (63.6%) were discharged with drainage under the supervision of polyclinic doctors. Four patients (36.4%) who had regression of the abscess cavity had their drainage removed before discharge. There were no cases of lethal outcomes in our study group.

Discussion

There is limited data on liver abscesses in patients who had a coronavirus infection, and is mostly reflected in a few publications of clinical cases. We present an analysis of case histories of 11 patients. There is a wide range of biochemical alterations that are seen in patients with COVID-19[2]. COVID-19 associated hepatic injury is defined as ALT or AST exceeding 3 times the upper limit of the normal value; ALP, GGT or total bilirubin exceeding 2 times the upper limit of the normal values and pathogenetically can be classified into hepatocellular, cholestatic and mixed type[13]. Signs and symptoms of gastrointestinal disease are common in patients who had COVID-19. A study by Weng et al. showed that 52 (44%) of 117 patients had gastrointestinal complications after a coronavirus infection, including anorexia, nausea, diarrhea, bloating, belching, vomiting, abdominal pain, and bloody stools[14]. In comparison, in all of our patients the prevailing complaints were abdominal pain and hyperthermia. Abnormal liver function tests and liver injury can develop during the next two weeks of hospitalization in up to 76.3-93% of patients[15,16]. However, in our group of patients liver transaminases were typically 2 times the upper limit of normal value.

The easiest imaging modality to diagnose liver abscess is USG due to its wide accessibility, low cost and time-efficiency. However, the sensitivity of USG is 85% compared to 97% of CT[17]. This depends on several factors including experience of the personnel, size of the lesion and technical parameters of the device. In our study group all abscesses were visible during USG, CT and MRI examination. However, the minimal size of the abscess in our study group was 2 cm.

Treatment of patients with liver abscesses includes antimicrobial therapy together with mini-invasive procedures such as percutaneous drainage/aspiration or in some cases surgery[18,19]. USG-guided drainage is the optimal treatment strategy with empirical antibiotic therapy followed by correction of antibiotic therapy in case of inefficiency or results of culture and other modalities. All of our patients undergone percutaneous drainage under USG guidance. The proposed method should be the golden standard since surgical procedures should be reserved for individual cases. As we demonstrate in our study percutaneous drainage is mini-invasive, allows to obtain material for culture and provides time for rational antibiotic therapy. In the current study patients were assessed based on their clinical picture, laboratory results followed by USG and another imaging technique (CT and/or MRI). Drainage was possible in all cases, patients received empirical antibiotic therapy and the abscess was sanitized using antiseptic solutions daily. However, there is limited evidence-based guidelines on liver abscesses in the literature[20]. Moreover, COVID-19-related liver abscess are described in the literature mostly as case reports. Sharma and coworkers report that in their group of patients with pyogenic liver abscess (before COVID-19 period) percutaneous aspiration was required in 27.8% of cases, percutaneous catheter drainage in 43.1% and surgery in 15.5% of cases[11]. Surgery is often considered a risky procedure especially in the settings of a pandemic[21]. The main indications for drainage are: left lobe abscess, thin rim (less than 10 mm) of hepatic parenchyma, multiple abscesses, rupture, nonresponse to medical therapy after 3-5 days[20]. Antibiotic therapy should be initiated after drainage (or blood culture is septic patients)[22]. Initial antibiotic therapy usually includes a third-generation cephalosporin and metronidazole or piperacillin/tazobactam. The selection of therapy should be based on in vitro antimicrobial resistance testing and clinical response[22]. The current standard of treatment in the institution was based on empirical treatment with cefoperazon with sulbactam. None of the patients required additional treatment and the results of antimicrobial studies corresponded to the treatment. Patients who develop liver abscesses typically have predisposing factors such

as diabetes mellitus, immunosuppression, malnutrition, advances age or alcohol consumption[20]. Other risk factors may include current malignancy, liver-transplant, end-stage renal disease, and cirrhosis[9]. Glycated hemoglobin level more than 7% and systemic problems assessed by Charlson Comorbidity index are predictors of severe course of the disease and poor outcome[23]. An important point in this study is that none of the patients had any diagnosed comorbid conditions, therefore, were considered healthy at admission. This underlines an important pathogenic mechanism of immune suppression in patients with COVID-19[24]. There is severely decreased expression of adaptive immunity-related genes that may lead to secondary infections[25]. The current study brings to light clinical evidence that patients are susceptible to infection after their COVID-19 recovery period.

Ferry et al. in 2020 presented a clinical case of a patient with a purulent liver abscess who recovered from COVID-19. Liver abscess is an extremely rare disease with an annual incidence of 2.3 cases per 100,000. The authors believe that all medical professionals, in particular surgeons, should be aware not only of the typical respiratory symptoms of COVID-19, but also of possible extrapulmonary manifestations of this disease[26].

Liemarto et al. published a clinical case report of a liver abscess with necrosis in a patient with a history of SARS-CoV-2. The team of authors state that the pathophysiological causes of liver injury after COVID-19 are: direct cytotoxicity of SARS-CoV-2; immune-mediated injury due to Systemic Inflammatory Response Syndrome (SIRS); hypoxemia and vascular changes due to coagulopathy, endotheliitis or congestion due to right ventricular failure and drug-induced liver injury[19]. It is important to mention that the prevalence of chronic liver disease in patients with COVID-19 is 2-11% and can be overlooked[16,27,28]. However, all of our patients had screening for infectious disease of the liver, which were negative in all cases. Some comorbidities that are common in the population are also frequently seen in COVID-19 and are associated with liver damage such as diabetes, hypertension, obesity and cardiovascular disease[29]. Interestingly besides the commonly known risk factors such as diabetes mellitus and end stage chronic kidney disease two of our patients had endophthalmitis. Endophthalmitis is considered a rare complication, however, it has increased during COVID-19 epidemic[30]. One of the major risk factors in eye surgery, especially vitrectomy and the predominant infectious agent is Streptococcus spp. It is important to assess the patient comprehensively taking into account all the systems[31].

Portal vein thrombosis is a rare but serious complication, which is more commonly seen in underlying disease such as cirrhosis, malignancies, pancreatitis, systemic autoimmune disease, and hypercoagulable states. The diagnosis of this complication and any accompanying reason is challengeable, while rapid diagnosis and treatment are essential[32]. One of our patients had portal vein thrombosis which resolved during the treatment period with anticoagulant therapy. The true nature of this event is hard to assess as the patient had no other comorbid conditions, but had a large multilocular abscess. Therefore, a combination of the proinflammatory state together with infection from the liver abscess and COVID-19 induced hypercoagulable state may be the explanation.

Patients with severe COVID-19 may develop Hypoxic-Ischemic Liver Injury. A study by Zhong et al. showed that liver ischemia-reperfusion can activate Kupffer cells, neutrophils and platelets, causing cellular destructive reactions that lead to inflammation and damage to the liver. Violation of microcirculation due to damage to the sinusoidal cells of the liver endothelium will also exacerbate liver ischemia and oxygen deficiency[33].

Hypoxia and inflammation are common in patients with severe COVID-19, which play an important role in the regulation of hepatocellular ACE2 expression. This explains the cause for the extrapulmonary dissemination of SARS-CoV2 in patients with acute respiratory distress syndrome (ARDS) and hypoxia. Hypercoagulability in patients with COVID-19 also contributes to liver damage with the occurrence of pulmonary thrombotic complications, which exacerbates acute right ventricular failure caused by high pulmonary vascular resistance in ARDS and leads to liver congestion[34]. Overall, it seems that liver injury during SARS-CoV-2 infection is most likely multifactorial, including direct cytopathic effect of the virus, systemic immune response, vascular damage and coagulopathy and drug-induced liver injury[6,35].

A variety of pathogenic organisms can be isolated from liver abscesses of patients with COVID-19 such as: Pseudomonas aeruginosa, Escherichia coli, Fusobacterium nucleatum, Entamoeba histolytica, Actinomyces israelii and other[18,19,36-38]. In our study all patients had Klebsiella pneumonia liver abscess and additionally in two cases Escherichia coli. The pattern of antibacterial resistance suggests that overall the bacteria were sensible to most of the available antibiotic therapy. None of the patients required step up therapy for their treatment regimen.

Autopsy studies demonstrate that patients who died of COVID-19 had histologic findings of macrovesicular steatosis and acute hepatitis combined with mild portal inflammation[39]. Most likely, the combination of the above factors and pathophysiological processes led to the formation of liver abscesses in our group of patients. However, despite the small number of scientific papers and insufficient understanding of all the morphological changes that occur in patients after COVID-19 the true nature of these cases is difficult to assess. There were no lethal outcomes in patients diagnosed with liver

abscesses. All 11 patients presented were discharged in a stable condition. The analysis of the available data and experience with this group of patients lead to the development of a clinical algorithm (**Table III**).

The main limitation of the current study is small number of cases. However, the present study represents a single center experience and one of the first attempts to analyze a group of patients with liver abscesses after COVID-19 infection from a clinical, radiological and surgical perspective.

Table III: Treatment algorithm of patient with SARS-CoV2-induced liver abscesses.

Obligatory steps	Possible complementation	Comments
COVID-19 test (PCR, IgM, IgG) History of liver disease Clinical picture of liver damage	---	Evaluation of COVID-19 status, past infections and past history of liver disease
USG of the liver	CT and/or MRI with contrast enhancement	CT with intravenous contrast enhancement should be performed for differential diagnosis and in complex abscesses MRI should be performed in cases when the biliary tract is suspected to be involved
Laboratory markers of liver function (ALT; AST; total, direct, indirect bilirubin, ALP) Laboratory marker of inflammation (CRP, leukocytes)	Oncological markers (AFP) Parasites (Echinococcus and other epidemiologically significant agents)	Other conditions which mimic liver abscess should be excluded
Drainage/aspiration of the abscess Assessment of antimicrobial resistance	Cytological evaluation	Cytological evaluation should be performed in cases when malignant conditions are suspected
Multidisciplinary approach	Telemedicine	Since this group of patients often have different comorbidities it is important to correct any metabolic, cardiovascular, kidney or other derangements

Conclusions

Patients with COVID-19 may develop liver abscesses, most likely due to direct damage to cholangiocytes, by binding of coronavirus to angiotensin-converting enzyme 2 receptors. Another important factor is a change in the immune status against the background of a systemic infectious and inflammatory disease in these patients. Moreover, patients with severe COVID-19 may develop hypoxic-ischemic liver disease. It is important to perform thorough diagnostic evaluation of the liver in patients who present with fever and/or abdominal pain after coronavirus infection. The patients should undergo complex evaluation due to comorbidities (metabolic and renal diseases). Further prospective studies are needed, including morphological evaluation of liver changes especially during autopsy. The current study demonstrates that percutaneous drainage, sanitation of the cavity combined with empirical antibiotic treatment is the optimal treatment modality for this group of patients.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at Botkin Hospital, Moscow.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Acknowledgments

None

Conflicts of Interest

None

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