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Idiopathic Liver Abscess Through Pseudomonas Aeruginosa and Bacteroides Fragilis in A Covid-19 Patient

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1. Abstract

1.1. Background & Aims: SARS-CoV-2 is well known to cause respiratory diseases and hyperinflammation – but it may also affect other organs like the brain, liver and heart. Different case reports have shown the possibility of an abscess emerged through COVID-19, but until now, none has been reported to be localized in the liver.

1.2. Case Report: After a holiday stay in Egypt, an 87-yrs.-old Caucasian male patient developed an aggravating dyspnea due to COVID-19 pneumonia leading to hospital admission. In the further course, elevated liver enzymes were observed. Sonography and computed tomography showed an extended liver abscess (through *Pseudomonas aeruginosa* and *Bacteroides fragilis*) which was treated by drainage and antibiotics.

1.3. Conclusions: In severe cases of COVID-19, hyperinflammation may cause immunodeficiency and bacterial superinfection such as liver abscesses. Sonography and computed tomography showed no source of the pyogenic liver abscess so that we assume a hematogenic spread of a pulmonary bacterial superinfection. Elevated liver enzymes and reduced laboratory markers for liver synthesis are a warning sign for a severe progress of COVID-19 with potential multi-organ dysfunction syndrome and for the complication of a pyogenic liver abscess.

As far as we know, we describe the first case of an idiopathic liver abscess, probably originated through a bacterial superinfection with *Pseudomonas aeruginosa* and *Bacteroides fragilis* during a COVID-19 disease.

2. Introduction

The pandemic spread of the SARS-Coronavirus-2- (SARS-CoV-2) is one of the most important medical and economic challenges of the last decades. By now (09/15/2021), we reached the line of having more than 250 million cases with over 4.65 million deaths world-wide and still, we do not know all of the virus' effects onto the human body [1].

The COVID-19 shows up with fever, dry coughing, sour throat, a

runny nose, dyspnea and general weakness, but there are more unspecific symptoms like vomiting, diarrhea or stomach-, head- and muscle pain as well [2]. In addition to these flu-like symptoms, anosmia and dysgeusia have become specific symptoms to distinguish the illness from a simple cold [3]. Furthermore, neurological symptoms have been described including stroke [4,5].

The use of a nasopharyngeal swab seems to be the most reliable way to detect the virus but RNA can also be found in human feces, urine and sewage [6,7] and even in the heart after endomyocardial biopsy [8]. Attempts to detect SARS-CoV-2 in the gall fluid have not been successful until now. Although the virus is not accumulated in the cerebrospinal fluid [9] it is assumed that the variety of neurological symptoms - besides stroke - is caused by axonal transport of the pathogen via the cribriform plate adjacent to the olfactory bulb [4]. Because most of the patients present themselves with respiratory symptoms, the World Health Organization (WHO) divides up the progress of the disease into "mild" (40% of all patients), "moderate" (40% of all patients), "severe" (15% of all patients) and "critical" (5% of all patients) depending on the manifestation [10]. While the moderate and severe level is represented by patients with pneumonia, the critical patient develops an Acute Respiratory Distress Syndrome (ARDS) and/or septic shock [10]. A multi-organ dysfunction syndrome and generalized inflammation is the final common path and bacterial co-infection/superinfection and the immune response is a central factor which determines the outcome of the patient [11-13]. Pathogenetically, Sars-CoV-2 enters the alveolar epithelial cells via attachment to the *angiotensin-converting enzyme 2-receptor* (ACE-2-receptor) [14,15]. Therefore with this specific receptor on their surfaces, different organs – like the heart, liver, brain, pancreas, or the kidneys – are possible targets [15,16].

After entering the cell and uncoating the virus' RNA is implemented into the host cells' DNA and virus particles and cytosolic proteins are produced. New virus proteins are produced by the host cell to be set free *via* exocytosis to infect other cells nearby. These proteins mediate a caspase induced pyroptosis with decline of the host cell, realizing cytokines and damage-associated molecular patterns (DAMPs) into the blood [2]. As a consequence, an excessive acute inflammatory response – often described as a 'cytokine storm' – effects the permeability of blood vessels and causes a marked vasodilatation; resulting in an ARDS, septic shock or multiorgan dysfunction syndrome in critical cases [2,17]. Different risk factors for the development of severe cases have been identified: The most common are older age, chronic lung disease, cancer, hypertension, diabetes and coronary heart disease [16,18,19], but there is also evidence that changes in liver associated laboratory data (hypalbuminemia, prolonged prothrombin time and elevated liver enzymes) forecasts severe cases and higher lethality [2,16]. Furthermore a bacterial superinfection is one of the serious complications in severe courses [20,21] with a mortality rate of 16% [22] in comparison to 2% - 5% of patients with COVID-19 in general [23]. As mentioned above, the liver may be affected as part of COVID-19 but scientific data are missing whether co-infections of the biliary tract and abscess formations are more likely with COVID-19. Usually, pyogenic abscess is a consequence of biliary infections or infections of organs drained by the portal vein - such as appendicitis or inflammatory bowel disease [24]. The bacterium that is to be found the most in drained liver abscess is E. coli, if a biliary origin is underlying. E.coli is often multidrug-resistant and only one part of a mixed infection [25]. Therefore, the pyogenic liver abscess is a rare but life threatening complication with a mortality rate of 6-19% [24]. The following case report is about an idiopathic liver abscess whose emergence is associated with COVID-19 and without a proof of an underlying alternative gastrointestinal disease.

3. Case Report

An 87-yrs.-old Caucasian was admitted March 28th, 2020 by his family doctor with a confirmed COVID-19 infection after a holiday stay in Egypt. The male patient had returned from the trip on March 10th back to Germany. A mild cough started on March 20th, while a nasopharyngeal sample was collected three days later and showed a positive result for Sars-CoV-2. On March 25th, the patient developed an aggravating dyspnea and initially felt relief after inhaling his salbutamol spray which he uses barely in case of an asthma attack. The progress of dyspnea had been the reason to call the ambulance. Regarding the previous co-diseases, the patient had a well-adjusted hypertension treated by ACE-inhibitor (Ramipril 5 mg once a day) and non–dihydropyridine calcium channel blocker (Verapamil 60 mg twice a day). In addition, his home medication was 100 mg of acetylsalicylic acid (ASA) as protection against a possible coronary heart disease and betahistine for the treatment of intermittently dizziness. In the past, a radical prostatectomy was performed because of a prostate cancer. With an BMI of 25.7 kg/m² the patient was at the edge of being overweight. Despite of his age, the patient was still physically active and went for snorkeling during his stay in Egypt. In our emergency room the patient presented himself oriented, normotensive (120/80 mm Hg) with normal heart rate (90 bpm) and mild elevated temperature of 38°C. Despite of an elevated respiratory rate of 22/min, the peripheric oxygen saturation was 98 % without application of additional oxygen. Both lungs were normally ventilated, the physical examination presented no further anomalies including the abdomen. The patient had no pain during examination. Electrocardiogram showed sinus rhythm without signs of ischemia in the terminal segments. The blood sample showed a high level of c-reactive protein (CRP) with 28.7 mg/dL (< 0.5 mg/dL) and an elevated procalcitonin (PCT) with 1.2 ng/ml (< 0.5 ng/ml). The leukocyte level was 16 x 10^3/µl with a differentiation of decreases lymphocytes (only 7%) and elevated segmented granulocytes (81%) and monocytes (11%). Additionally, the patient's liver enzymes were elevated with gamma-glutamyl transferase (GGT) of 203 U/l (< 71 U/l), alanine transaminase (ALT) of 76 u/l (< 50 U/l) and total bilirubin level of 1.48 mg/dl (< 1.2 U/l). As marker for liver synthesis, our laboratory's COVID-19-protocol included INR and PTT, which

were nondescript, but D-dimer was elevated with 3.6 µg/ml (< 0.5 µg/ml). Levels of albumin, fibrinogen and aspartate-aminotransferase were not tested; renal markers and troponin were not elevated.

The chest x-ray demonstrated peripheral infiltrates in the lower parts of both lungs. Because of the elevated procalcitonin an antibiotic therapy with ampicillin/sulbactam (3 g every eight hours, intravenously) and bronchodilatory therapy with salbutamol and atrovent (four times a day) was started. Furthermore, supportive care with breathing exercises and mobilization by physiotherapists was started. In the blood cultures from March 28th 2020, *Bacteroides fragilis (B. fragilis)* was found which was sensitive to initiated antibiotic therapy. Legionella antigen (urine) and antigen levels of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (serum) demonstrated no evidence of an atypical pneumonia. Because of an increasing CRP and persistent fever after 2 days of antibiotic therapy, we conducted an abdominal ultrasound on March 30th. Here a centrally located isoechogenic lesion with cystic elements with a diameter of 55 mm was found in the liver – rated as potentially malignant - as well as several small liver cysts. The lesion showed no typical sonographic aspect of an abscess. In the consequence the antibiotic therapy was switched to piperacillin/tazobactam (4.5 g every six hours, per day) due to persistent fever and, after a temporary suspicion for an allergic reaction after the first dosage, we chose meropenem (1 g every six hours, per day). The same day, the patient suffered from aggravating dyspnea, so that we ran another thorax x-ray that showed progressive bipulmonal consolidations. Because of temporary respiratory rates > 30/min we decided to transfer the patient to our intensive care unit (ICU) for observation. Due to a respiratory failure the patient had to be intubated in the night of the 2nd to April 3rd. The laboratory data is representing the severe situation with a PCT of 8.99 ng/ml, a CRP of 29.52 mg/dl and 22.2 x 10^3/µl total leucocytes. The GGT has risen from 203 U/l to 379 U/l (< 71 U/l) without elevation of the total bilirubin or the further liver enzymes. PTT and Quick (INR) were at normal level, but the total protein was decreased with 4.46 g/dl (norm: 6.6 – 8.7 g/dl). In the consequence the antibiotic therapy was expanded by ciprofloxacin. The makers for infection decreased and the respiratory situation re-improved the next 3 days so that extubation of the patient followed on 6th of April. The next day, he could be retransferred to our isolation ward. After two negative test results for Sars-CoV-2 isolation could be removed. On April10th the blood sample showed rising CRP- and GGT- levels again as well as an impaired coagulation with an INR 1.56 (> 0.85-1.25), but no fever or decline of the former condition. Another abdominal ultrasound was performed: By then, the central lesion of the liver with former malignant aspect now showed signs of an abscess with increasing size (diameter of 75 mm). The formations previously diagnosed as liver cysts were septate at this point and showed enlargement as well. The following computed tomography (CT) of the abdomen confirmed the suspected diagnosis of several liver abscesses, so that we placed a 19 F-pigtail catheter under sonographic control without complications and preserved putrid secretion. CT showed no further sources of an abdominal infection, especially the colon was inconspicuous except a diverticulosis. The procedure was conducted in general anesthesia because of the former diagnosis of COVID-19 and the assumed possibility of a reactivation. Another testing for COVID-19 via nasopharyngeal swab was negative. In the evacuated pus *Pseudomonas aeruginosa* (*P. aeruginosa*) was found besides the same *B. fragilis* that was already detected in the blood culture, but we could not find RNA of SARS-CoV-2 in the sample. The current antibiotic therapy with ciprofloxacin was stopped and metronidazole was added. By combination of meropenem and metronidazole, infection parameters fell properly. Two samples of tracheal secretion were negative for bacterial isolates after microbiological cultivation (unfortunately collected after the use of antibiotics). Due to the history of travel to Egypt, the serum levels of amoeba-antibodies were determined which showed a negative result.

On April10th, the patient suffered from pain in the right upper abdomen and rising liver enzymes including spontaneous elevation of INR as well as a decreased level of Hemoglobin (Hb) from 10.7 g/dl to 8.0 g/dl. The patient was transmitted to the ICU again and a second CT showed a rupture of the liver with the pigtail catheter still placed inside the abscess. Because of the alternated blood coagulation due to acute liver failure a Prothrombin complex concentrate (PCC) and a pair of red blood cells (RBCs) were substituted. After consulting the surgical department of University Hospital Muenster, a conservative treatment was decided. On April 14th, another CT of the abdomen was conducted after 800 ml of blood were extracted from the pigtail catheter, showing a dislocation of the catheter and a beginning subcapsular necrotic process of the liver rupture. Therefore, the patient was transferred to the Department of Surgery, University Hospital Muenster on April 15th 2020 for CT-guided placement of drainage into the abscess (Figure 1). A surgical intervention of the rupture was discussed, but the initial organization of the hematoma underlined the possibility of a conservative procedure. After re-transfer to our ICU the next day, we stopped treatment with meropenem and used metronidazol and high-dose ceftazidim based on the susceptibility testing of isolated species originating from the previous drainage sample. Neither in the first nor in the second sample we found any evidence of the SARS-CoV-2 particles, but the already known *B. fragilis* species and *P. aeruginosa* - both without acquired antibiotic resistance. After three days we released the patient from the ICU because of decreasing laboratory parameters (leucocytes, CRP). CT and sonographic controls verified the regression of the liver abscess (Figure 2). After the treatment of a cardiac decompensation with diuretics (heart failure known for years and therefore probably not associated with COVID-19), the patient was discharged on May 7th 2020. In the further follow-up of 16 months, he did not develop any signs of reinfection or recurrent liver abscess.

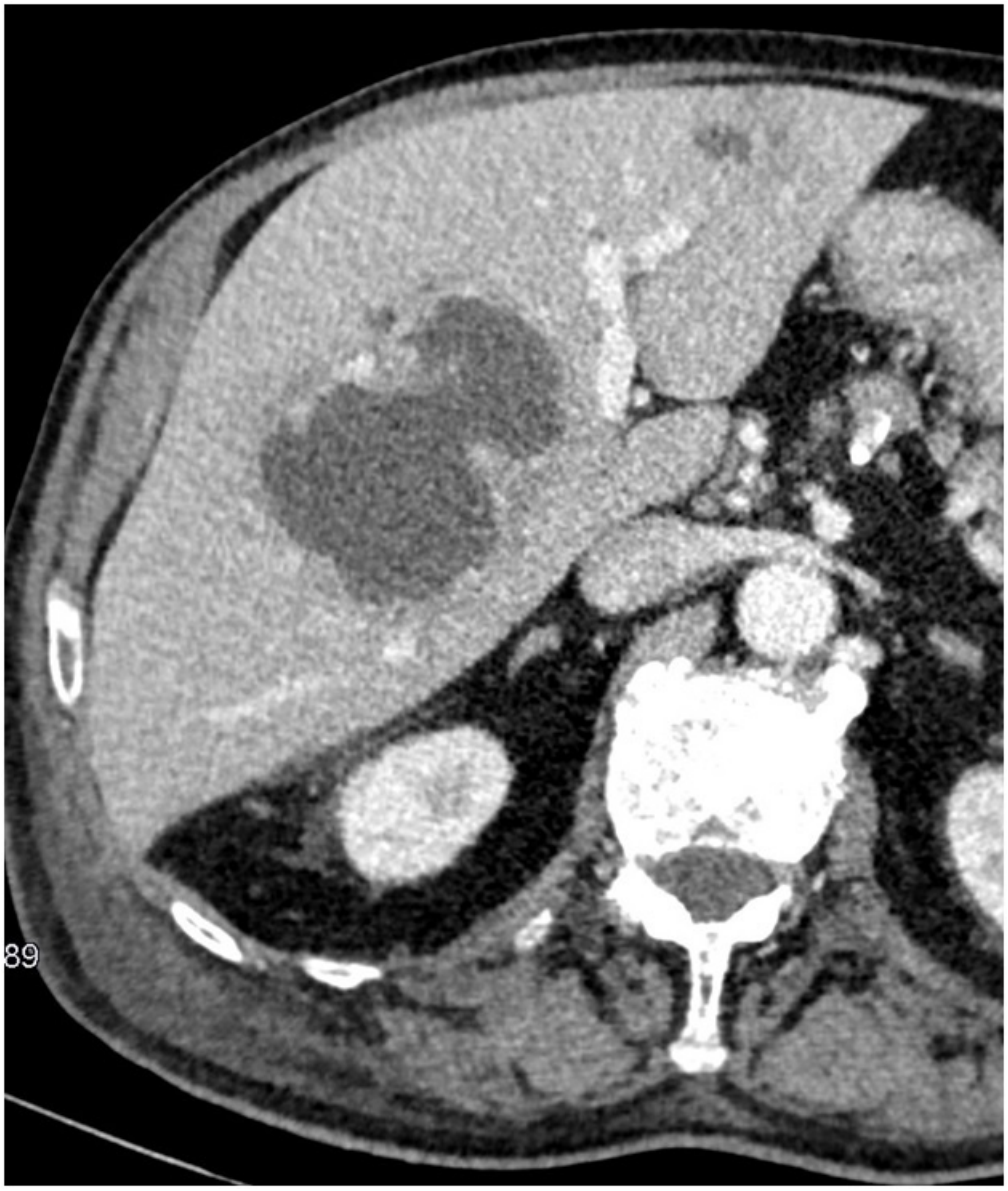
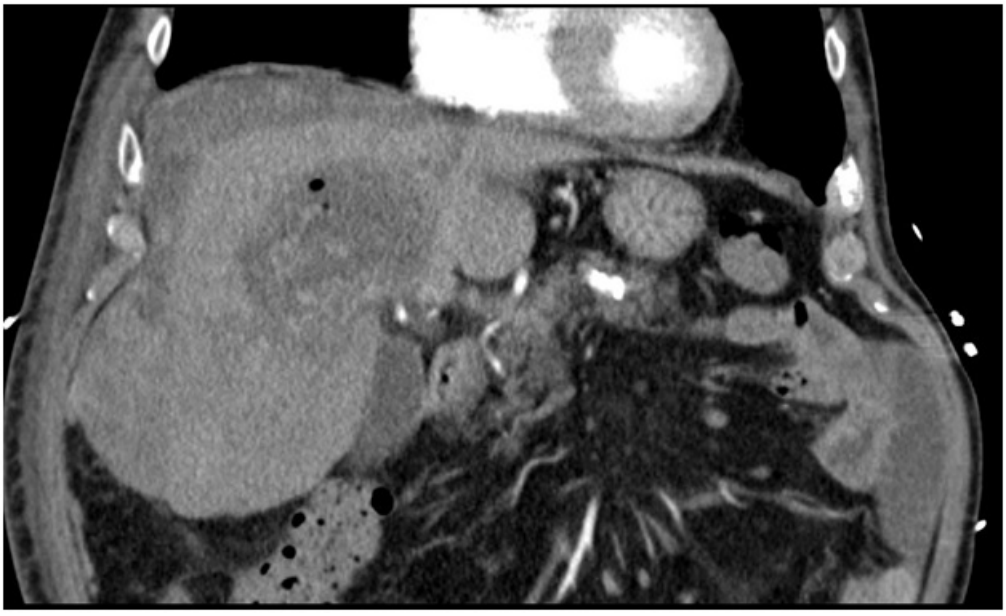


Figure 1: CT scan of liver abscess.



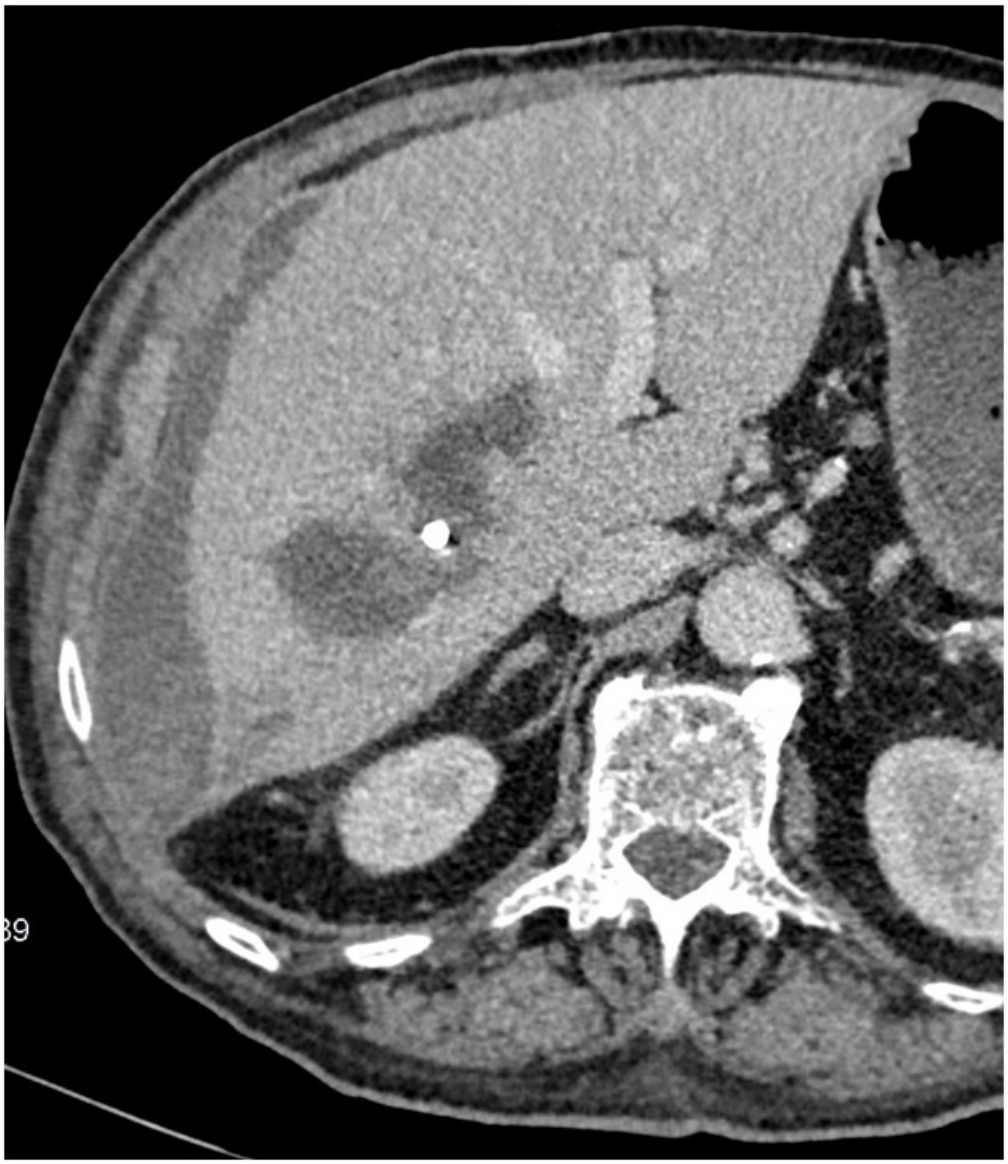


Figure 2: CT scan of liver abscess after successful drainage.

4. Discussion

To our knowledge, COVID-19 presenting with a liver abscess is unreported until now, although it is unclear if SARS-CoV-2 is coincidental or a contributing factor to the pathogenesis in this case. The PCR of the liver abscess aspirate was negative with respect to SARS CoV-2-virus. To our knowledge, there is no report of a successful testing the virus' RNA in gall fluid until now. On the other hand, the occurrence of an abscess in the context with a COVID-19 infection has been reported, but not yet inside the gastrointestinal tract [21,26-29].

There are different hypothesis how the liver may be damaged in COVID-19: SARS-CoV-2 uses the ACE-2-receptor to enter into the cell of the respiratory tract, that is also expressed in the liver [15]. Chai *et al.* showed that SARS-CoV-2 affects the cholangiocytes and causes a dysfunction with consecutive liver injury what can be measured by GGT-elevation [11,30]. Alternative ways of cellular liver damage in severe and critical COVID-19 cases are via anoxia (e.g. in septic shock) as well as the cellular damage as a consequence of used hepatotoxic antiviral drugs during the therapy of COVID-19 and/or a reactivation of a pre-existing liver disease [31,32]. Furthermore, hyperinflammation induced by SARS-CoV-2 may damage organs through the activation of macrophages and natural killer cells comparable to the local hyperinflammation in Langerhans cell histiocytosis or to pathophysiological reaction in a severe burn injury [33-35]. But not every infection with SARS-CoV-2 may lead to an involvement of the liver or elevated liver enzymes: Skevaki *et al.* suggested that the severity of COVID-19 infection and the capacity of liver synthesis on one hand and severity of the infection and level of the liver's acute phase proteins on the other hand are correlated: The more severe the infection proceeds the lower is the level of Albumin and Fibrinogen and the higher is the increase of Ferritin, INR, CRP and Procalcitonin [36]. In their meta-analysis, Henry and colleagues pointed out that elevated liver enzymes come along with elevated Troponin and renal biomarkers in critical cases at a stage of a multi-organ dysfunction syndrome [37]. Especially upregulating of Ferritin is associated with severe cases and higher lethality; amounts of > 2000 μg/L have been

found in non-survivors in Wuhan [16,23,38]. As mentioned above, an elevated level of PCT is a prognostic marker for severe cases as well, although there exists no evidence that PCT elevation is based on COVID-19 or else as a sign of a bacterial superinfection [37,39]. The triggers for releasing PCT are usually bacterial lipopolysaccharides (LPS) and toxins as well as the host's inflammatory cytokines, while in viral infections secreted interferon-γ (IFN-γ) stops the rise of procalcitonin [40]. That is why we rated the elevated PCT level in severe cases as bacterial superinfections. Thus, the liver is involved and affected directly in severe cases of COVID-19 and elevated acute phase proteins are a warning sign for increased lethality. In our case the patient showed lymphopenia and elevated infection rates including a PCT of 1.2 ng/ml (< 0.5 ng/ml) and a CRP of 28.7 mg/dL (< 0.5 mg/dL) already at the beginning as a sign of a potential severe case. PCT was rising up to 8.99 ng/ml and, analogous to Skevaki et al. low albumin level [36], the total protein was decreased with 4.46 g/dl (norm: 6.6 – 8.7 g/dl) when he had to be intubated because of respiratory failure three days later. An impaired coagulation had not been detected at the beginning, but in the course when the abscess proceeded. Ferritin has not been tested at any time. Furthermore, GGT was already elevated in the emergency room representing advanced stages of the disease with an involvement of the liver as well. But at what point SARS-CoV-2 and the resulting abscess deranged the GGT as a combination of two pathologies is uncertain. Summarizing, laboratory data fulfilled the criteria for a severe case of COVID-19.

But why do severe and critical cases tend to bacterial co-infections? One reason might be that bacterial co-infections appear more likely in hospitalized patients with SARS-CoV-2 as nosocomial pneumonia [41]. Because of the valuable healthcare recourses, mild and even moderate cases are treated in an ambulatory setting and, therefore, secondary nosocomial bacterial infections appear in the advanced stages of COVID-19 when the patient is hospitalized.

Furthermore, we know that the immune response is an important factor in COVID-19 disease which determines the outcome of the patient: SARS-CoV-2 affects the epithelium of the respiratory tract via using ACE-2 as a surface receptor for entry, a protein that is also to be found in different organs all over the human body [30,42]. If the disease proceeds, DMAPs and cytokines mediate a cytokine storm with the consequence of an ARDS and/or septic shock with multi-organ failure [11]. This process ends up in an immune dysregulation with lymphopenia and low cell counts of natural killer cells [43]. Therefore, patients with severe cases of COVID-19 suffer under a immunodeficiency and thus are in danger of a bacterial superinfections, what might abet the development of an abscess. Although there is no research about the risk factors or general probability to develop an abscess during a COVID-19 disease yet, we assume that a pyogenic abscess will develop much more likely in severe cases than in mild or moderate ones. This is affirmed by the research of bacterial superinfection in severe cases of influenza in the pandemic of 2009, where severe courses showed more bacterial superinfections and thus more complications with greater use of healthcare resources, and increased risk of death [44]. To our mind, this could be comparable to infections with the SARS-CoV-2: In a review about bacterial co-infections Rawson *et al.* reported as well, that only 8% of patients with COVID-19 suffer on a bacterial or fungal superinfection [41], but if they do, the mortality rate rises up to 16% [22] in comparison to 2% - 5% of patients with COVID-19 in general [23]. It should be noted that a bacterial co-infection increases morbidity and mortality and thus the use of adequate antibiotics is of high importance. Astonishingly, the bacteria we found in the pus after aspiration biopsy were *P. aeruginosa* and *B. fragilis*. *B. fragilis* belongs to the intestinal flora and is a potential germ for intestinal infections or abscesses [45]. *P. aeruginosa* on the other hand is an opportunistic pathogen, that causes mainly nosocomial infections like ventilator-associated pneumonia or catheter infections in immunocompromised patients [46]. It is a rare pathogen in liver abscesses, but cases with *P. aeruginosa* have been reported [47]. Usually the pyogenic liver abscess is a consequence of biliary infections or infections of organs drained by the portal vein [24], but with different diagnostic tools at different times, there had not been any sign for an abdominal infection or anamnestic hints for an infection before. While the *B. fragilis* could have ascended of the intestine out of its natural habitat, the source of the *P. aeruginosa* is unclear. The bacterium has been found neither in the blood cultures nor in the tracheal secretion, but that could be due to the usage of antibiotics before testing. We assume that the primary infection with *P. aeruginosa* was ventilator-associated when the patient was extubated because of respiratory failure. In the next step, it could had been transmitted via bloodstream [48] to the preformatted liver abscess, which has been caused by the *B. fragilis*. The hyperinflammation with its relative immunodeficiency might have favored the origin of the abscess as we mentioned above. In this case the patient suffered from a further complication of liver abscess - a rupture after drainage. Due to the high mortality caused by surgery, the primary strategy, whenever possible, is conservative treatment which was successful in this patient. Only in the situation of severe uncontrolled hemorrhage, laparotomy with abdominal package of the liver should be performed [49].

The liver is at risk to be injured through SARS-CoV-2 in severe cases and elevated liver enzymes and reduced laboratory markers for liver synthesis are warning signs for the involvement of the liver. The patient can suffer of bacterial co- and superinfections. Therefore, routine laboratory and sonographic controls of the abdomen should be done to identify a progress of COVID-19 and potential complications like the liver abscess described in this case report.

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