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CASE REPORT

Clinical characteristics and management of a liver transplanted patient admitted with SARS-CoV-2 infection



Andrea De Gottardi^{a,d,g,*}, Corneliu Fratila^b, Raffaella Bertoli^c,
Andreas Cerny^d, Lorenzo Magenta^d,
Pietro Gianella^b, Pietro Majno-Hurst^{e,g}, Alessandro Ceschi^{c,g},
Gianluca Vanini^b, Enos Bernasconi^f

^a Division of Gastroenterology and Hepatology, Ente Ospedaliero Cantonale, Ospedale Italiano, Lugano, Switzerland

^b Division of General Internal Medicine, Ente Ospedaliero Cantonale, Ospedale Italiano, Lugano, Switzerland

^c Division of Clinical Pharmacology and Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale, Lugano, Switzerland

^d Epatocentro Ticino, Lugano, Switzerland

^e Division of Visceral Surgery, Ente Ospedaliero Cantonale, Ospedale Civico, Lugano, Switzerland

^f Division of Infectious Diseases, Ente Ospedaliero Cantonale, Ospedale Civico and Ospedale Italiano, Lugano, Switzerland

^g Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland

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COVID-19;
Immunosuppression;
Low-dose CT scan;
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Summary We present here the case of a 62-year-old man, who was referred to the emergency department with fever and cough for 3 days. He underwent liver transplantation 4 years earlier due to HCV and NASH-related cirrhosis with hepatocellular carcinoma. At admission he was in reduced general conditions. Nasopharyngeal smear specimen resulted positive for SARS-CoV-2 infection. Pulmonary low-dose CT-scan revealed bilateral subpleural ground-glass infiltrates. O₂ saturation was 93%. A treatment with lopinavir/ritonavir and hydroxychloroquine twice daily was started. The patient received also cefepime and remained in isolation. Seven days later imaging showed a progression of the pulmonary infiltrates. Cefepime was replaced

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BP, Blood Pressure; COVID-19, CoronaVirus Disease 19; GGT, Gamma Glutamyl-Transferase; HCV, Hepatitis C Virus; HR, Heart Rate; NASH, Non-Alcoholic Steatohepatitis; PCR, Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2.

* Corresponding author at: Gastroenterology and Hepatology, Ente Ospedaliero Cantonale, Ospedale Italiano, Via Pietro Capelli 1, 6900 Lugano, Switzerland.

E-mail address: andrea.degottardi@eoc.ch (A. De Gottardi).

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by meropenem. During the following 3 days the fever resolved, and the general conditions of the patient significantly improved. Consequently, treatment with lopinavir/ritonavir and hydroxychloroquine was stopped. The evolution of SARS-CoV-2 interstitial pneumonia in this immunosuppressed patient was moderate to severe and liver injury was not clinically significant. Despite its limitations, this case report confirms that the liver may be only mildly affected during SARS-CoV-2 infection, also in liver transplanted patients. Further studies are needed to assess whether the outcome of SARS-CoV-2 infection is worse in immunosuppressed patients than in the general population.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) outbreak has originated in China in December 2019 [1,2] and [3]. As of 20th March 2020, the reported cases worldwide were 209839, in Europe 87108, in the United States of America 7087, with globally 8778 virus-related deaths [4] and is increasingly affected by the epidemic [5].

Respiratory failure from acute respiratory distress syndrome is the primary cause of mortality, although other clinical manifestations including gastrointestinal manifestations. Currently, the management of COVID-19 is supportive, therefore there is an urgent need for effective specific treatments. Preliminary observations suggest that patients with cardiac diseases, hypertension, or diabetes are at higher risk of severe disease [6], while mortality risk factors for SARS-CoV-2 infection include advanced age, high SOFA score, and D-dimers greater than 1 µg/mL [7]. There is currently an urgent need for data about COVID-19 in solid organ transplant recipients, because immunosuppression may be associated with a more severe disease course and outcome. Data are arising in kidney transplantation [8,9], but no information is available in the liver transplant population.

Case description

On 4 March 2020, a 62-year-old man presented to the emergency department with fever and cough for 3 days. He underwent liver transplantation 4 years earlier for HCV genotype 1 and NASH-related cirrhosis with hepatocellular carcinoma. The patient had sustained virological response after HCV treatment with daclatasvir and sofosbuvir before transplantation and was positive for anti-HBc alone. The patient was overweight and suffered from type 2 diabetes, arterial hypertension and dyslipidemia. His regular medication included sirolimus, mycophenolate mofetil, gliclazide, metformin, vildagliptin, valsartan, amlodipine, rosuvastatin, bisoprolol, and entecavir.

At admission the patient was in reduced general conditions, with body temperature 38.5 °C, BP 125/70 mmHg, HR 92/min. Pulmonal and cardiac auscultation were normal. C-reactive protein was 18 mg/L, ALT was minimally increased (57 IU/L) and AST, GGT, alkaline phosphatase and bilirubin were in normal range, glucose 6.3 mM, hemoglobin 133 g/L,

leucocytes 5.1 G/L. Urinary Legionella and pneumococcal antigens were negative. Multiplex PCR for respiratory pathogens in the nasopharyngeal swab was negative.

PCR test of a nasopharyngeal smear specimen resulted positive for SARS-CoV-2 infection. Whereas conventional lung X-ray did not show any pathological findings, pulmonary low-dose CT-scan revealed bilateral subpleural ground-glass infiltrates (Fig. 1A).

In the arterial blood gas analysis while breathing room air at a respiratory rate of 20/min pO₂ was 9.4 kPa (normal range 11.1–14.4), O₂ saturation 93%, bicarbonates 20 mM (normal range 22–26).

Although the vast majority of reported COVID-19 cases are acute and resolve rapidly, the disease can also manifest itself with severe symptoms and be fatal in up to 3% due to extensive alveolar damage and respiratory failure [10]. Therefore, due to the potential clinical efficacy for COVID-19 patients [11] and based on SARS clinical cases in 2003 [12], and before the publication of the LOTUS China trial [13], we started a treatment with lopinavir 200 mg and ritonavir 50 mg 2-0-2, and hydroxychloroquine 200 mg twice daily. The patient also empirically received cefepime and remained in isolation. Since ritonavir is a strong CYP3A4 inhibitor, sirolimus was decreased by 50% and plasma levels were monitored daily to maintain a 4–8 µg/L range. Amlodipine and rosuvastatin were stopped.

Clinical data available so far indicate that up to 53% of the patients with COVID-19 present increased levels of transaminases during the infection and that liver injury is apparently associated with the severity of respiratory symptoms [14,15]. In our patient however, only ALT was minimally increased at admission and normalized subsequently, while all other liver function tests remained within normal range.

Due to persistent fever ranging between 37.5 and 39.0 °C, mild deterioration of the respiratory function with pO₂ 8.1 kPa, increasing CRP (182 mg/L), and diarrhea, CT-scan imaging was repeated 7 days after the first imaging and confirmed the suspicion of progression of the pulmonary infiltrates (Fig. 1B). Cefepime was replaced with meropenem. All blood cultures were negative, as well as *Clostridium difficile* toxin and PCR for enteric pathogens in stool samples, and *Aspergillus* sp. galactomannan.

During the following 3 days the fever resolved, CRP decreased to 54 mg/L, oxygen saturation increased to 94%

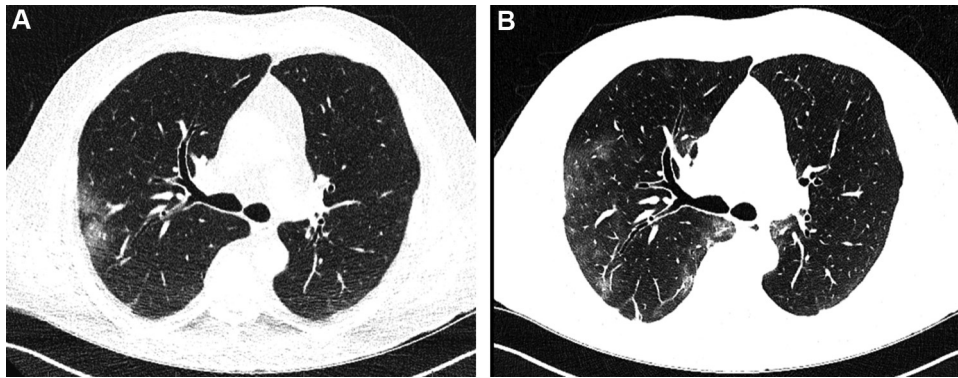


Figure 1 CT-scan images at admission (A) and after 7 days of antiviral treatment (B). At admission the patient presented with bilateral subpleural ground-glass infiltrates that were also present in the left lower lobe. In the CT-scan performed one week later, the infiltrates were significantly progressing, not only in the subpleural regions, but also to both lower lobes (not shown).

and the general conditions of the patient significantly improved.

Consequently, treatment with lopinavir/ritonavir and hydroxychloroquine was stopped and the patient continued recovering clinically.

Immunosuppression with sirolimus was increased to the usual dose of 1 mg/day and transaminases always remained within the normal range.

Discussion

We present here the first case of SARS-CoV-2 infection reported in the literature in a liver transplanted patient. In this immunosuppressed patient, the evolution of the infection was characterized by a moderate to severe interstitial pneumonia over a period of 10 days with a minimal initial increase of ALT. In terms of CT imaging, the evolution of the infiltrates in this patient was similar as the one reported in non-immunosuppressed patients [16,17] or in patients treated with lopinavir/ritonavir [18]. Different treatments are currently being tested in patients with severe forms of SARS-CoV-2 infection, including tocilizumab and remdesivir [19,20]. Recent data indicate that the treatment with lopinavir/ritonavir is not associated with a significant decrease in mortality compared to supportive care [13], although the authors reported that the between-group difference in the median time to clinical improvement (15 days vs. 16 days) was significant. Whether in this immunosuppressed patient this treatment was somehow effective remains arguable, but these medications certainly exposed the patient to the risk of significant drug interactions and toxicity. Currently available data are insufficient to ascertain whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2 [21]. Moreover, hydroxychloroquine was reported to have activity in vitro against the SARS coronavirus [22], but its potential clinical efficacy on SARS-CoV-2 remains to be demonstrated.

We discussed the option of starting a treatment with tocilizumab, an interleukin-6 inhibitor, in the case of worsening of the symptoms, although there is no efficacy or safety data yet to support its use in COVID-19 patients. A mul-

ticenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of pneumonia due to SARS-CoV-2 infection is currently ongoing [23]. Moreover, remdesivir, an adenosine nucleotide analog developed against Ebola virus disease [24] has been found to have antiviral activity against SARS-CoV-2 and is currently tested in a phase 3 clinical trial [25].

The findings presented here confirm that the liver may be only mildly affected during SARS-CoV-2 infection and suggest that this is also true in liver transplanted patients.

Ethics

Informed consent was obtained from the patient.

Data accessibility statement

The data that support the findings of this study are available from the corresponding author, upon request.

Disclosure of interest

The authors declare that they have no competing interest.

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