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BILATERAL POLYSEGMENTARY PNEUMONIA CAUSED BY SARS-COV-2 IN A TRANSPLANTED LIVER RECIPIENT

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Background*. In December 2019, the humanity met a previously unknown infectious disease (COVID-19) caused by a new coronavirus called SARS-CoV-2. An important role in the treatment of COVID-19 belongs to anti-inflammatory and immunosuppressive drugs. In this regard, the cases of the disease in patients undergoing long-term immunosuppressive therapy, for example, organ transplant recipients, are of particular interest. We present our clinical observation of COVID-19 in a liver recipient patient, which, apparently, is the first in the Russian Federation.* ***Clinical case description*** *A 54-year-old man, 10 years ago at the A.I. Burnazyan Center underwent transplantation of the right lobe of the liver after resection of hepatocellular carcinoma, T2N0M0, and due to liver cirrhosis as a result of HCV hepatitis. At the time of hospitalization, he had been constantly receiving immunosuppressive monotherapy with everolimus. The patient was transferred to an infectious disease hospital due to a positive PCR test for SARS-CoV-2 RNA. No signs of respiratory failure were found upon admission. Subsequently, a mild course of COVID-19 was observed, without signs of an acute inflammatory reaction, with normal CRP values and a slight increase of ferritin. 7 days after the treatment, the patient was discharged for outpatient observation.* ***Conclusion.*** *This clinical case is of interest not only by the success of the treatment of the new coronavirus infection COVID-19 in an immunocompromised patient — a recipient of a liver transplant, but also by the fact that the disease manifested itself primarily as a transient increase in hepatic aminotransferases, which can be attributed to the gastrointestinal manifestations of COVID-19.*

Keywords: *SARS-CoV-2, COVID-19, organ transplant recipients, liver transplant.*

(***For citation:*** Ischenko RV, Golovinskiy SV, Akhmedyanov AR, Voskanyan SE, Kolyshev IYu. Bilateral Polysegmentary Pneumonia Caused By SARS-COV-2 in a Transplanted Liver Recipient. *Journal of Clinical Practice.* 2020;11(2):101–206. doi: 10.17816/clinpract35121)

BACKGROUND

In December 2019, humankind faced a previously unknown infectious disease COVID-19. The clinical presentation of COVID-19 is manifested by a severe acute respiratory syndrome (SARS), therefore the new coronavirus was named SARS-CoV-2 [1–3]. Drug therapy for this viral disease is exclusively empirical, and its efficiency is still controversial [4, 5]. Anti-inflammatory and immunosuppressive drugs play a certain role in the treatment of COVID-19 [6, 7]. In this regard, cases of the disease in patients undergoing long-term immunosuppressive therapy, for example, organ transplant recipients, are of particular interest. The first clinical cases of the course of COVID-19 in such patients (recipients of heart transplants) were followed-up undoubtedly in China [8]. In the international scientific medical literature, as of May 14, 2020, we revealed one publication of a series of COVID-19 cases in organ recipients from the USA [9] and no more than 10 clinical cases from other countries. We present our clinical case of COVID-19 in a patient with a liver transplant, which was apparently the first in the Russian Federation.

CLINICAL CASE

The patient's data

A man, 54 years old, was urgently transferred from the A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency of Russia to our Center (Federal Research and Clinical Center of the Federal Medical and Biological Agency of Russia) with complaints of dry cough, fever up to 38.5°C, and general asthenia.

The anamnesis shows that in 2010, at the A.I. Burnazyan Federal Medical Biophysical Center, the patient underwent living-related transplantation of the right lobe of the liver after removal of hepatocellular carcinoma T2N0M0 in presence of liver cirrhosis as a result of viral hepatitis C. At the time of hospitalization, the patient was constantly receiving immunosuppressive monotherapy with everolimus at a dosage of 4

mg/day. Control of the C0-concentration of everolimus in the blood before the transfer was 6 ng/ml. Therapy with an inhibitor of mTOR receptors was chosen in the early post-transplant period due to severe nephrotoxicity and the stage II chronic kidney disease (glomerular filtration rate according to the CKD-EPI formula was 62 ml/min/m^2) while taking calcineurin inhibitors (tacrolimus, cyclosporine).

At the end of March 2020, during a routine examination for a transplanted organ, according to a biochemical blood test, high levels of hepatic transaminases were detected, and therefore on April 6, 2020, the patient was hospitalized at the Center for Surgery and Transplantology of the .I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency of Russia with a provisional diagnosis of liver transplant dysfunction.

A plain radiograph of the chest organs dated 04/07/2020 revealed infiltrative changes in the C4–5 view on the left. On April 8, 2020, a trephine biopsy of a liver transplant was performed. The histological examination showed F1 fibrosis according to Metavir, A0–1 activity, mild venulitis; and no signs of transplant rejection were revealed. According to the results of computed tomography (CT) of the abdominal cavity and chest from 04/14/2020 in the segments 3, 6, and 10 of the left lung and in the segments 6, 7, and 10 of the right lung, areas of ground glass opacity infiltration of various degree of intensity and consolidation of lung tissue, fields of cord–like thickening, and minor reticular changes (Fig. 1).

Clinical diagnosis was bilateral multisegmental viral pneumonia.

In view of the CT scan data, the patient was isolated in a boxed ward, after which he underwent a nasopharyngeal smear analysis for the presence of SARS-CoV-2 RNA by the polymerase chain reaction (PCR) method. On April 16, 2020, he had dry cough and an increase in body temperature up to 38.0°C. On April 17, 2020, a positive PCR test was obtained for the presence of SARS-CoV-2 RNA. The patient was transferred to a specialized hospital to continue the treatment.

Upon admission, the patient's condition was satisfactory, with the body temperature of 38.4°C and finger pulse oximetry 96% in atmospheric air. Repeated test of a smear from the mucous membrane of the oropharynx by PCR at the time of the patient's admission confirmed the presence of SARS-CoV-2 virus RNA.

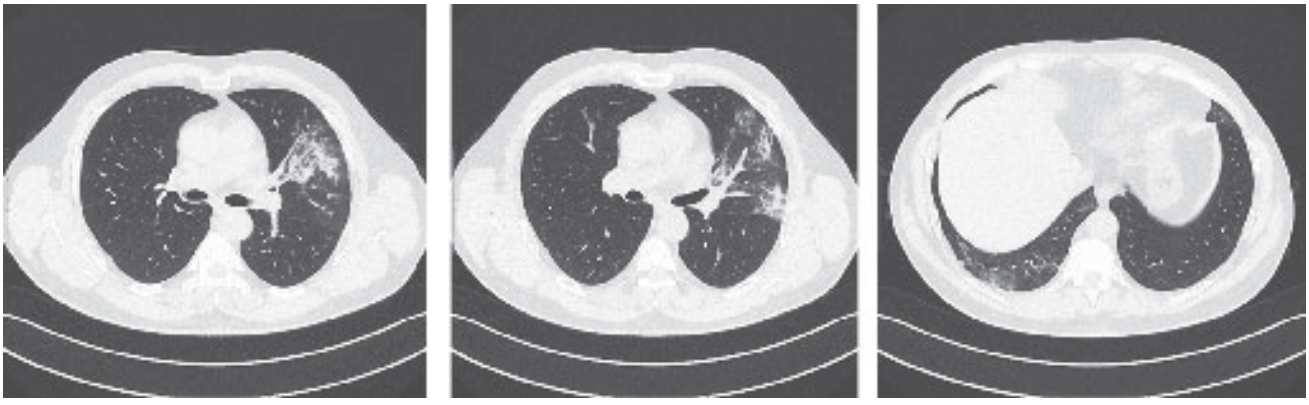
Instrumental and laboratory diagnostics

According to laboratory blood tests, lymphopenia was detected in presence of moderately increased ferritin and normal level of C-reactive protein, as well as an increase in the levels of gamma glutamyl transpeptidase, alkaline phosphatase in presence of normal values of bilirubin and hepatic transaminases (Table 1).

Treatment

Drug therapy was prescribed in accordance with the recommendations of the Ministry of Health of the Russian Federation, namely hydroxychloroquine at a dose of 200 mg 1 time a day per os (the dosage was reduced relative to the protocol and amounted to 400 mg 2 times a day, due to a history of drug damage to the kidneys and a high level of hepatic transaminases); azithromycin 500 mg 1 time a day per os, cefoperazone/sulbactam 2.0 mg 1 time a day intravenously, clexane 0.4 ml subcutaneously 1 time a day, infusion intravenous therapy with crystalloid solutions in a volume of 1000 ml a day. In addition, the patient continued the intake of the immunosuppressive drug (everolimus) at the same dosage of 4 mg a day per os, as well as individually selected antihypertensive and basic antiulcer therapy.

Fig. 1. Patient, 54 years old: data of computed tomography of the chest organs from April 14, 2020 in the course of a routine examination.



https://doi.org/10.17816/clinpract35121

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Table 1

Changes of laboratory parameters over time (biochemical blood test)

Indicator	Bed-days of inpatient treatment			
	1	3	6	7
Gamma glutamyl transpeptidase, U/l	134	161	179	173
Alkaline phosphatase, U/l	188	118	191	183
C-reactive protein, mg/l	5,8	-	-	3,8
Leukocytes, $\times 10^9$/l	3,71		4,97	6,01
Lymphocytes, n, $\times 10^9$/l	0,86	0,75	-	0,91
Total protein	57	-	-	-
Ferritin	390,7	-	-	457,3
Bilirubin	7,2	-	-	9,7
Alanine aminotransferase	27	33	-	45
Aspartate aminotransferase	23	23	-	36

Dynamics and outcomes

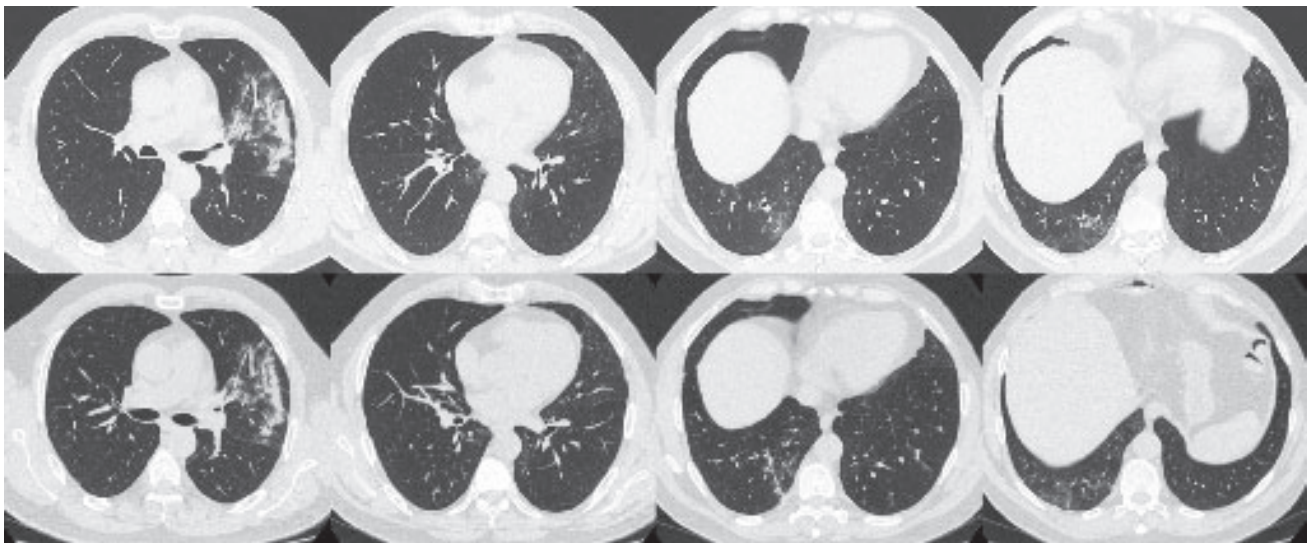
Starting from the day 2 of inpatient treatment, the body temperature was normalized. A control laboratory study showed an insignificant increase in the dynamics of gamma-glutamyltransferase and alkaline phosphatase, and therefore, given the absence of fever and the reference level of C-reactive protein in the blood serum (Table 1), antibacterial therapy with cefoperazone/sulbactam was canceled.

Control PCR studies of a smear from the mucous membrane of the oropharynx on the days 5 and 7 of inpatient treatment did not reveal the presence of SARS-CoV-2 virus RNA. The results of CT scan of the chest organs from 04/24/2020 showed a positive tendency and a decrease in the foci of ground glass opacity (Fig. 2). Considering the patient's stable condition, the absence of fever and laboratory markers of an acute inflammatory reaction, as well as a two-fold negative PCR test result for SARS-CoV-2 RNA, on the day 10 of inpatient treatment, the patient was discharged for outpatient follow-up treatment with recommendations to continue immunosuppressive therapy under control of the drug concentration.

DISCUSSION

This case demonstrates the need for an individual approach to each patient admitted to an infectious diseases hospital, especially after organ transplanta-

Fig. 2. Patient, 54 years old: data of computed tomography of the chest organs from April 24, 2020, in the course of the treatment.



tion. The presented case is interesting in the fact that a confirmed new coronavirus infection was detected in a patient receiving immunosuppressive therapy for liver transplantation; and the clinical, radiological, and laboratory symptoms were consistent with the diagnosis of COVID-19.

Currently, the impact of previous immunosuppressive therapy on the course of COVID-19 is underinvestigated, and SARS/MERS recommendations have not been validated due to the short duration of the epidemic with limited cases. The need for glucocorticosteroids for mild COVID-19 is controversial. There is also concern that reducing or discontinuing of immunosuppressive therapy may cause acute graft rejection. A position document of the European Associations for the Study of the Liver (EASL) and Clinical Microbiology and Infectious Diseases (ESCMID) recommends not to reduce immunosuppressive therapy for COVID-19 [10].

The optimal management of transplant immunosuppression in the COVID-19 setting is also a subject of ongoing debate. Similar to other viral infections, reduction or discontinuation of mycophenolate mofetil has been recommended [11]. A 2012 study showed that replication of human coronaviruses depends on intact immunophilin pathways and can be inhibited by tacrolimus. Our multidisciplinary team recommended that the patient continue to take everolimus, both to protect the graft function and to prevent exacerbation of the inflammatory response to viral infection.

One of the works described a longer detection of the virus in patients with a mild form of COVID-19 infection without significant deterioration in the underlying disease [12]. To date, it is clear that the disease of our patient has not progressed to a severe form associated with hyperimmune reactions, probably due to his immunocompromised status.

Further randomized controlled clinical trials of the course and virological clearance of COVID-19 in organ transplant recipients undergoing immunosuppression will be valuable in optimizing treatment approaches.

CONCLUSION

This clinical case demonstrates the successful recovery of a liver transplant recipient with COVID-19 pneumonia during immunosuppressive therapy with everolimus. This case is of interest not only by the success of treatment of an immunocompromised patient-recipient of the transplanted liver, but also by the fact that the disease onset was manifested primarily by a transient increase in the levels of hepatic aminotransferases, which can be attributed to the gastrointestinal symptoms of the new coronavirus infection COVID-19.

INFORMED CONSENT

Written voluntary informed consent was obtained from the patient for the publication of the clinical case description (date of signing 06/06/2020).

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

Funding source. The study had no external funding.

AUTHOR CONTRIBUTIONS

R.V. Ishchenko, S.V. Golovinsky, and A.R. Akhmedyanov wrote the text of the article, searched for literary sources; S.E. Voskanyan, I.Yu. Kolyshev performed the analysis of literature data and proofreading of the article. All authors made a significant contribution to the search and analytical work and preparation of the article, read and approved the final version before its publication.

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https://doi.org/10.17816/clinpract35121

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