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CASE REPORT

LIVER TRANSPLANTATION FROM SARS-COV-2 INFECTED DONOR IS STILL A CONTRAINDICATION? A CASE REPORT OF A SUCCESSFUL LIVER TRANSPLANTATION FROM A SARS-COV-2 INFECTION DECEASED DONOR TO VACCINATED RECIPIENT AND REVIEW OF THE LITERATURE

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Summary

Pandemic risks sustained by the Severe Acute Respiratory Syndrome Corona-Virus 2 (SARS-CoV-2) have a negative impact on solid organ transplantation activity worldwide. The donor-derived infection risk for immunosuppressed recipient impacted negatively on organ donation and transplant activity, due to its possible unfavorable prognosis. In the difficult pandemic scenario, also the transplant community faced the problem according to the new evidences about SARS-CoV-2 infection and its related risks.

National Transplant Community firstly allowed the organ transplantation from SARS-CoV-2 infected donor only in case of emergency, when patient survival in waiting list could compromised the prognosis quoad vitam.

Vaccination campaign and the possibility for risk categories to have an extra booster dose, help the transplant candidate to create a good immune coverage against community contagious risk but also against donor-derived risks infection.

In this case we describe a successful liver transplantation from a donor died for secondary cause of SARS-CoV-2 to a recipient with a positive history for SARS-CoV-2 infection and two doses of vaccine.

In the case described, there was considered the hypothetical risk of donor-derived infection risk from SARS-CoV-2. Nevertheless, urgent hepatic transplantation was motivated by the very serious prognosis of the recipient on the active list, and the recipient was protected by specific, circulating, and cell-mediated immunity. Post-operative course was uneventful.

Considering the many clinical experiences included the one described, we suggest to review the indication for organ allocation in case of organs coming from SARS-CoV-2 deceased donors.

Key words: SARS-CoV-2, immunodepression, immunosoppressive risks, liver, liver transplantation, organ procurement, infective risk, SARS-CoV-2 donor

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INTRODUCTION

Since December 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pathologic agent of COrona VIrus Disease-(20)19 (COVID-19) has spread worldwide. COVID-19 has been declared a pandemic by the World Health Organization (WHO) on 11 march 2020.
SARS-CoV-2 global pandemic drastically impacted on National Health Care systems included Solid Organ Transplantation (SOT) programs which have been forced to temporarily stop their department's activity. The lack of scientific evidences about the risk of SARS-CoV-2 for transplanted patients and patients in waitlist, is one of the problems that Transplant physicians have still to face. Many other studies are needed to seek understand this infectious disease.
Considering evidence of increased mortality from SARS-CoV-2 infection among patients with multiple comorbid conditions, consequences of infection among waitlist patients may be serious.
The current recommendations are based on assumption that SARS-CoV-2 could be transmitted to the recipient through SOT and resulting in severe manifestations in immunosuppressed patients.
Nevertheless, the actual risk of donor-derived transmission of SARS-CoV-2 in transplant recipient is still unclear. Italian national guidelines recommend routine testing of donors for SARS-CoV-2.
Deferral of all donors who test positive for SARS-CoV-2 may result in the loss of a considerable number of otherwise medically suitable life-saving organs for liver transplantation (LT). The adhesion to such a restrictive policy could be lethal for critical recipients, and therefore the uncertainty of the theoretical possibility of donor to recipient SARS-CoV-2 transmission, may be preferable to the alternative of death on waiting list [1,2].
In Italy, recipients listed for liver and heart transplantation, SARS-CoV-2 positive, or with a previous history of COVID-19 disease, can be transplanted with organs from SARS-CoV-2 positive deceased donors. In this case, the local transplant team decide if the recipient is in severe clinical conditions, that lead to a high estimated waitlist mortality or a low probability of a timely, suitable, non-infected match.
Transplant candidates must receive appropriate counseling before accepting organ from SARS-CoV-2 donor including potential risk of transmission and consequences associated with COVID-19 disease developing.
Anyway, even if as of now, SARS-CoV-2 donor-derived transmission has been reported only in lung transplantation [9,10], it is not yet clear whether is suitable to use organs from donors SARS-CoV-2 positive.
Even more so, it is unclear if is suitable to use organs from donors deceased from COVID-19 disease.
Hereby we described the first case, at our knowledge, of successful LT from a donor died from the consequences of COVID-19 to a recipient with a recent history of COVID-19 and successively SARS-CoV-2 vaccinated.

CASE DESCRIPTION

Donor

We were contacted by the Italian National Transplant Center (CNT) for a potential liver donor, deceased from hemorrhagic complications secondary to SARS-CoV-2 infection.
The donor, a 61-year-old man (weight: 90 kg; height: 175 cm; body mass index: 29.39), blood group 0 Rhesus positive, with no previous significant medical history, was admitted the 21/07/2021 in a context of pneumonia and severe acute respiratory syndrome, secondary to SARS-CoV-2 infection. SARS-CoV-2 positivity was defined as a positive result on real-time polymerase chain reaction (RT-PCR) assay of naso-pharyngeal swab (NPS) specimen and bronchoalveolar lavage (BAL).
He had no previous medical history of COVID-19 nor of SARS-CoV-2 vaccination and was treated with standard therapy according to Italian Pharmacologic Agency (AIFA) guidelines for admitted patients (December 2020 guidelines). Nevertheless, clinical conditions worsened and he was initially treated with Extra Corporeal Membrane Oxygenation but developed relentlessly an acute respiratory distress syndrome and progressive multiple organ dysfunction syndrome and disseminated coagulopathy.
He died the 11/08/2021 from cerebral hemorrhage.
The patient gave consent to organ donation through the Italian Transplant Informative System register of consent.
The risk assessment of the donor was evaluated by a multidisciplinary team and the CNT give to the donor an acceptable non-standard risk which defined a donor acceptable for recipient in life-threatening conditions (CNT Guidelines for evaluation of donor eligibility and specific protocols, revision of 01/03/2005).

Recipient

He was a 64 years-old man, blood group 0 Rhesus positive (weight: 82 kg; height: 170 cm; body mass index: 28.4), with an end-stage non-alcoholic steatohepatitis -related cirrhosis and Model for End-stage Liver Disease (MELD) of 29, Child-Turcotte-Pugh score B9 and hepatic-renal syndrome type 2. He has a medical history of type 2 diabetes, overweight and arteriosus hypertension.
On January 2020, he developed SARS-CoV-2 pneumonia with pulmonary microembolism. He had standard therapy according to AIFA guidelines for admitted patients. During hospitalization, he developed a first episode of cirrhosis decompensation with ascites and anasarca. He left

hospital the 03/02/2021 after two weeks with negative RT-PCR for SARS-CoV-2 on NPS.
He was listed for LT on 22/07/2021 because of the persistence of his refractory ascites and the worsening of medical conditions.
He received the first dose of COVID-19 mRNA vaccine Pfizer® mRNABNT162b2 (Comirnaty®) the 18/06/2021 and an additional dose the 16/07/2021.
The recipient completed screening procedures and spirometry showed moderate restrictive ventilatory impairment and severe reduction of diffusing capacity of lung for carbon monoxide of 49%. Chest angio-CT didn't show features compatible with COVID-19 or pulmonary micro-embolism so those spirometry alterations were attributed to a right elevated hemi-diaphragm and an associated hepato-pulmonary syndrome.
Cause of the rapid decline of patient clinical conditions, implying a greatly high risk of death, we decide to accept the organ offer.
The day of LT, SARS-CoV-2 RT-PCR on NPS was negative and neutralizing SARS-CoV-2 antibodies were protective: IgG against receptor binding domain (RBD) > 130; IgG antiS1 > 220, IgG antiS2 > 100, IgG against nucleocapsid positive [3].
Whole size LT was performed the 12/08/2021 with standard piggy-back technique. Cold ischemia time was 7 hours and 20 minutes and warm ischemia time was 30 minutes. Surgical procedure was completely uneventful. Based on our center protocol, the recipient received induction immunosuppression, at unclamping and reperfusion, with Basiliximab 20 mg, methylprednisolone 500 mg intravenously. The maintenance therapy with mycophenolate mofetil 500 mg twice daily and tacrolimus with target trough levels of 6-8 ng/dl was started in second post-operative day (POD). The patient was extubated on the first POD. No acute rejection episode was observed.
The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peak was at POD 1 with values respectively of 3585 U/L (normal values 0-40 U/L) and 1824 U/L (normal values 0-40 U/L). International Normal Ratio (INR) peak was at POD 1 with value of 1.29. The graft showed rapid recovery after LT and patient clinical course was uneventful.
The patient was discharged from Intensive Care Unit (ICU) on POD 5 without any SARS-CoV-2-related symptoms and without any chest radiological features suggesting for COVID-19 infection. SARS-CoV-2 NPS was realized on POD 7, 14, 21 and 28 and were always negative. SARS-CoV-2 RNA on donor liver perfusion liquid was negative. We didn't perform liver biopsy.
SARS-CoV-2 test on urine and stools on POD 8 and 14 were also negative. Patient at POD 14 and 28 showed neutralizing SARS-CoV-2 antibodies: IgG against RBD > 130; IgG antiS1 > 220, IgG antiS2 > 100, IgG against nucleocapsid positive.
Patient was discharged from hospital on POD 14. At twelve months from LT patient is still alive and in good conditions, graft laboratory tests are optimal.

DISCUSSION

The COVID-19 clinical spectrum ranges from asymptomatic state to severe rapidly fatal disease. In Italy from February 2020 infected COVID-19 patients have grown to an exponential rate. Initially there was a growing concern about unfavorably implications in organ transplant and donation activities due to ICU bed restrictions, healthcare transplant professionals' diminution because employed in COVID-19 units, travel and working restrictions and therefore great impact on logistics for organ procurement and transplantation [4,5].
In addition, two scenarios appeared: the risk of donor-recipient viral transmission is not yet fully clarified and infection could potentially result in severe manifestations, in immunosuppressed patients.
Moreover, LT candidates with symptomatic SARS-CoV-2 infection were considered at high risk of early death, especially those with decompensates cirrhosis MELD score 15 [2-7].
On these bases, international transplant societies recommend against the use of organs from donors with active SARS-CoV-2 infection and recommend donor SARS-CoV-2 screening to prevent inadvertent positive organ transplant [7,8].
Unfortunately, the main consequence is the loss of a considerable number of otherwise medically suitable life-saving organs for transplantation and in fact, organ donation and transplantation have been reduced in many countries [1].
Globally, no SARS-CoV-2 transmission has been reported with organ transplantation except for three cases of donor to recipient proven SARS-CoV-2 transmission by lung transplantation despite pre-transplantation negative donor upper respiratory tract testing. The donors BAL result positive immediately after transplantation. One of these donors donated also kidney and liver without reported transmission of SARS-CoV-2 to the two kidneys end the one liver recipients [9-11].
At this point it was necessary to verify more precisely the impact of the clinical role of the virus in SOT.
Regarding LT, many studies investigated the virus impact and its mechanism of virulence in abdominal organs.
In case of LT, the risk of SARS-CoV-2 transmission may arise through expression of the SARS-CoV-2 receptor (angiotensin 2 converting enzyme receptor) by cholangiocytes and hepatocytes [12,13].
Anyway, the presence of only viral components in various tissues can be demonstrated with PCR in blood (from

1 to 15%), in stools (29%) and in urine (6.9%), but most published studies have not demonstrated SARS-CoV-2 in liver [14,15].

At our knowledge, only one publication reported viral-RNA in formalin-fixed tissue blocks. In that paper most patients who died of COVID-19 had evidence of mild focal hepatitis clinically and histologically. Nevertheless, compared with other organs, viral RNA of SARS-CoV-2 was less frequent in liver specimens and was detected in less than half of the cases [13].

However, the presence of intact SARS-CoV-2 virions, with possibility of replication and infection, can be confirmed only with viral culture and none of the published studies has performed viral culture to demonstrate the presence of transmissible virus. Therefore, it is not feasible to determinate whether organs and tissues viral transmissibility can actually be possible [16].

Moreover, there are no reports confirming transmission of other related coronavirus, like SARS-CoV or MERS CoV, through either transfusion or transplantation. Finally, there have been no proven or probable reports of any RNA respiratory virus, including influenza, transmitted to a non-lung organ transplant recipient [16].

However, hepatocellular injury has been reported in 14-53% of SARS-CoV-2 infected patients [18].

From the clinical point of view, the histopathological picture is represented by microvesicular steatosis and mild lobular and portal activity, nonspecific findings that might be consistent with multiple etiologies [18].

We have to consider that from 2 to 11% of the patients treated for COVID-19 have already underlying chronic liver disease [18].

None, nowadays, has yet demonstrate the exact impact of COVID-19 on liver function, resulting as an independent comorbidity on patient's outcomes [19].

As described by Yip TC-F et al., ALT/AST elevation seems to be common in COVID-19 patients but in fact generally moderate, although more severe increase can be observed in 78% of patients with symptomatic and severe forms and in patients requiring hospitalization in an ICU [20].

Other causes of liver injury should be evoked in these patients such as hypoxic hepatitis when there is a sudden raise of aminotransferases in ICU patients. An increase in AST may be related to myocarditis for example [19].

Some studies suggested that liver injury may be considered as a consequence of adverse drugs reactions and systemic inflammation and cytokine storm due to COVID-19 rather than direct virus-mediated injury of the hepatocyte [16].

For that reason, routinely diagnostic biopsy does not appear indicated [22].

Despite the dramatic impact of COVID-19 pandemic on organ donation and transplantation activity, Italy held better than other countries: comparing the Italian data with those of Spain, France and the United States, it emerges that in the period from February 28 to April 10 2020 the decrease in transplantation activity was 39.7% compared to 51.1% in the USA, 75.1% in Spain and 90.6% in France [6,23].

In 2020 the overall drop in organ donation and transplantation activity was 10%.

The decrease in donors used was 7.8% and that of transplants carried out was 6.6% compared to the previous year, 2019. In the same period, liver transplantation signed a decrease of 8.5% (CNT. Press Release N. 20/2020).

Conversely in 2021 the prompt reorganization of CNT network activity resulted in an increase of 12.1% in organ donation activity and 9.9% of transplantation activity. In particularly, in Italy, in 2021, 1376 liver transplantations were performed, 14.5% more than 2020 (CNT. Press Release N. 1/2022).

In fact, Italy was the first European country allowing the use of livers and hearts from donors with active SARS-CoV-2 infection, documented by positive nucleic acid testing in NPS or BAL at the time of donor evaluation (CNT, National Transplant Network. Report 2020).

These organs can be transplanted into informed recipients with ongoing or resolved COVID-19 [1].

On this issue, the WHO has established the criteria for healing with two negative NPS collected at least 24 hours apart [24].

Furthermore, in an update date 17/6/2020 two other possible criteria have been placed for diagnosis of healing. In both cases it was decided that a negative NPS test was necessary: in symptomatic subject, when ten days have passed since the beginning of the symptoms and three days after the disappearance of the symptoms and, in asymptomatic subject, when ten days have passed from the positivity of the test [25].

On the basis of those criteria, the Italian CNT (CNT. Press Release 19/01/2022, Prot 2042/CNT 2022) elaborated even more careful criteria for donor selection: the organs can be transplanted when 14 days have elapsed from virological healing with two negative NPS at least twenty-four hours apart and when BAL, carried out in the twenty-four hours, maximum forty-eight hours prior to organ procurement, were negative from the donor at the time of donation. A time interval from healing equal to twice the incubation time was thus chosen for greater protection against the risk of transmission. The specimens test of choice is nucleic acid test [26-28].

However, in order to comply with urgent life-saving organ transplant criteria, the Italian CNT decided that organs could be allocated even in case of a donor, tested positive for SARS-CoV-2 at the time of the organ procurement, as long as he had not died of viral causes and the recipient was an asymptomatic or pauci-symptomatic COVID-19 patient or in presence of a COVID-19 history in the previous four months or in a vaccinated patient (3 doses, the

last one not injected more than four months before organ offer) and with documented vaccine response (CNT. Press Release 9/2/2021).
The rationale behind this choice relies on the potential presence of circulating protecting antibodies and delayed cellular immunity preventing SARS-CoV-2 transmission or reactivation.
If post-transplant immunosuppression is not an absolute risk factor for COVID-19 associated mortality, age > 60 years, long-term recipients, metabolic-related comorbidities are responsible for the increased risk of this severe pathology [29].
Unfortunately, data on COVID-19 in SOT, and particularly in post-transplantation, are based on short and uncontrolled series with conflicting results. The incidence of COVID-19 in a large real-life Italian survey, was only 1.25%, and most patients (75%) had mild disease [30].
The candidates vaccinated against SARS-CoV-2 may make transplantation more acceptable even though it is known that the cirrhotic liver patient can have an insufficient response to vaccination and therefore cannot guarantee effective active immunity. The development of viral mutations, can escape the immunity created by the vaccine in use or the natural one. Furthermore, there are no reliable immunological data that the title of the antibody response and the degree of the consequent antibody protection can guarantee candidates for transplantation [1,31].
Trials to assess efficacy/safety of COVID-19 vaccines in liver disease are underway, but in patients on the waiting list the efficacy seems to be inferior as documented by the Italian Association for the Study of the Liver (AISF), indeed the antibody response at the end of the full course of BNT162b2 or mRNA-1273 antiSARS-CoV-2 vaccines is reduced from 31 to 47.5% [32], instead patients with histories of COVID-19 respectively seroconverted in 94% and 92% after the first and the second vaccine dose [33].
It is recommended that patients on liver transplant waiting list, also with a documented COVID-19 recovered, should be vaccinate with two doses of anti-SARS-CoV-2 mRNA vaccines, only after the complete disappearance of the clinical manifestations of the disease and after the end of the isolation period, and vaccination should be delayed for at least 90 days [31,32].
Our described case is part of a not much broader series of LT, performed in the SARS-CoV-2 pandemic period, with donor affected by COVID-19 in which the transmission donor-derived risk, is containable [34,35].
As described in Romagnoli et al study, in Italy, following CNT protocol, from November 2020 to May 2021, 17 livers from SARS-CoV-2 positive donors have been transplanted in recipients with ongoing or past COVID-19. The preliminary results in 10 recipients with a median follow-up of 5 months, were extremely positive. In fact, none of the LT recipients developed COVID-19 symptoms and 8 patients tested SARS-CoV-2 negative in post-LT period and the other two were positive before LT and became negative from postoperative day 28 [1].
In our case also, the LT was performed intentionally and the donor/recipient match showed that the donor died of serious complications from COVID-19 and the recipient had previous healed COVID-19 and two anti-SARS-CoV-2 vaccine doses (BNT162b2). Finally, he showed high neutralizing antibodies titer before LT and a favorable delayed immune response against SARS-CoV-2 via T cells, therefore LT seemed to be reasonable in an urgent life-saving liver transplant setting.
Considering the current limited published evidence, with this case report we don't want to suggest the necessity to reconsider for transplantation liver organs from donors who died of COVID-19 related reasons. However excessively restrictive policy could result in suitable organs lost, increasing waiting time and mortality. Urgent candidates, like our recipient, may not survive to receive another liver from a non-infected donor and the uncertainty of donor to recipient transmission of SARS-CoV-2 may be acceptable and preferable to the risk of recipient lost on waiting list. Therefore, our case may strengthen the emerging conviction that organs from active COVID-19 donors could be used for immune recipients and that a previous infection and/or vaccination may protect LT recipients from SARS-CoV-2 superinfection.
In the cohorts of liver transplant recipients, it will be necessary to carry out a personalized assessment in the management of SARS-CoV-2 infection with the help of increasingly updated behavioral guidelines that consider the possibility of obtaining and maintaining effective delayed cellular immunity, through an active vaccination policy.
Larger studies are needed to define clear guidelines.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

CP, MM, FD, EA: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; GB: acquisition data of recipient; PD, PM: Acquisition data of donor; MM, PM: drafting the work or revising it critically for important

intellectual content; EA: final approval of the version to be published; EA, MM: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical consideration

Not applicable.

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