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Clinical characteristics and immunosuppressants management of coronavirus disease 2019 in solid organ transplant recipients

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CT, computed tomography; HBV, hepatitis B virus; IVIG, human immunoglobulin for intravenous injection; MMF, Mycophenolate Mofetil; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; SpO_2, percutaneous oxygen saturation; TBIL, total bilirubin; TACE, transcatheter arterial chemoembolization; WBC, white blood cell; WHO, World Health Organization

Abstract

Over 1,000,000 cases of coronavirus disease 2019 (COVID-19) have been confirmed since the worldwide outbreak began. Not enough data on infected solid organ transplant (SOT) recipients are available, especially data about the management of immunosuppressants. We report two cases of COVID-19 in two transplant recipients, with different treatments and prognoses. The first patient received liver transplantation due to hepatitis B virus-related hepatocellular carcinoma and was confirmed to have COVID-19 nine days later. Following a treatment regimen consisting of discontinued immunosuppressant use and low-dose methylprednisolone-based therapy, the patient developed acute rejection but eventually recovered. The other patient had undergone a renal transplant from a living related donor 17 years ago, and was admitted to the hospital because of persistent fever. This patient was also diagnosed with COVID-19. His treatment regimen consisted of reduced immunosuppressant use. No signs of rejection were observed during the regimen. In the end, the patient successfully recovered from COVID-19. These effectively treated cases can provide a basis for immunosuppressant management of COVID-19-positive SOT recipients.

Keywords

COVID-19; Solid organ transplant recipient; Clinical characteristics; Immunosuppressant

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease, and the ongoing outbreak has been declared a pandemic and global public health emergency by the World Health Organization (WHO) [1–2]. As of April 1, 2020, a total of 937,151 cases had been reported in at least 200 countries [3]. Investigations are under way worldwide to better understand the transmission dynamics and the spectrum of clinical illness. Because they are a population living with immunosuppression, the identification, diagnosis, and clinical course of infected solid organ transplant (SOT) recipients may differ from those of the general population [4]. However, data on the clinical presentation and management in SOT recipients are insufficient, especially regarding the management of immunosuppressant. It is necessary to establish a system for treatment of COVID-19 in these patients. This report describes the clinical features and management of two COVID-19 cases in SOT recipients and may provide suggestions for immunosuppressant management.

Case report

Case 1

A 37-year-old man was admitted to the hospital on January 14, 2020, because of intermittent upper abdominal pain having lasted more than three months. He had a 19-year history of hepatitis B. After performing relevant examination and evaluation, the diagnoses of hepatocellular carcinoma and hepatitis B virus (HBV) infection were made. He underwent transcatheter arterial chemoembolization (TACE) on January 16, after which his body temperature rose to 38.3°C. Ceftriaxone sodium and tazobactam sodium were administered for treatment. He underwent liver transplantation on January 21. The pathogen tests of the donor including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were negative. The immunosuppressive therapy consisted of oral tacrolimus (dosage was adjusted according to the concentration of FK506) and intravenous methylprednisolone (300 mg initial dose, and then progressively decreased to 20 mg). On the ninth day after liver transplantation, he developed a fever with a peak body temperature of 38.6°C. Percutaneous oxygen saturation (SpO_2) was around 94%, accompanied by weakness, abdominal discomfort, and sleep disorders (Figure 1). Several tests were performed:

• The peripheral white blood cell count (WBC) was $2.46*10^9$/L, red blood cell count was $3.52*10^{12}$/L, hemoglobin was 118.6 g/L, platelets were $74*10^9$/L, lymphocyte count was markedly lower at $0.48*10^9$/L, the level of serum alanine aminotransferase (ALT) was 240 U/L, and total bilirubin (TBIL) was 38.9 μmol/L.

• A COVID-19-specific real-time polymerase chain reaction (RT-PCR) test was performed on nasopharyngeal aspirate and was confirmed positive.

• A pulmonary computed tomography (CT) scan showed multiple patchy ground-glass density lesions were seen in both lungs with multiple abnormalities in bilateral lungs (Figure 3A).

These abnormalities suggested the possibility of COVID-19 infection, so the patient was immediately transferred to the intensive care unit for isolation and observation. Treatments were administered in accordance with local practice for COVID-19 [3]. Oral tacrolimus was also suspended, and low-dose intravenous methylprednisolone was administered (40 mg, q12h).

Two days later, the patient's SpO_2 was greater than 96%. On February 3, the reviewed examination still showed positive COVID-19 RT-PCR results. In response to this, oseltamivir phosphate capsules, cefoperazone, and sulbactam sodium were maintained. Five intermittent COVID-19 RT-PCR rechecks all showed positive results. However, the symptoms of fever, weakness, abdominal discomfort, and sleep disorders were all alleviated. On February 8, the patient's body temperature was basically normal. The antibody test for COVID-19 showed levels of the IgM antibody were over 30 AU/ml, and the IgG antibody was 29 AU/ml. Both of these values were higher than baseline values. Moreover, pulmonary CT suggested the viral pneumonia was alleviated on February 14 (Figure 3B).

However, the bilirubin level became abnormal on February 17, with TBIL at 87.8 μmol/L, direct bilirubin 48.8 μmol/L, ALT elevated to 214 U/L, aspartate aminotransferase (AST) 122 U/L, and no fever developed. Since the tacrolimus had been suspended for two weeks, medical staff considered that the transplanted liver had begun to display the effects of rejection. For this reason, tacrolimus was administered (2 mg, q12h). Despite this, the serum TBIL level did not decline. It increased to 103.7 μmol/L, and ALT was 424 U/L on February 24. The patient was given large doses of intravenous methylprednisolone (300 mg for three days, progressively decreased to 20 mg). Finally, the acute rejection was under control, and the serum levels of TBIL, ALT, and AST declined gradually**.** However, after analysis of the patient's lymphocyte subtypes test, results

showed that the patient was immunosuppressed the entire time, the absolute T lymphocyte count was between 313/μl and 495/μl, B lymphocyte count was between 41/μl and 99/μl, and the ratio of Th/Ts lymphocyte was between 0.52 and 0.80. Re-examinations of the COVID-19 RT-PCR test after March 6 were all negative. On March 12, the patient was declared cured in accordance with clinical cure standards and discharged.

Case 2

A 48-year-old male patient was hospitalized on February 6, 2020, with the chief complaint of persistent fever for 10 days, with a peak temperature of 37.8° C, accompanied by cough, sputum, muscle aches, fatigue, and chest tightness. He was diagnosed with COVID-19 two days prior in the fever clinic, however, the treatment in clinic was not effective. The patient had received a living related donor renal transplantation in 2003 due to renal failure, and was taking oral immunosuppressants regularly after surgery (tacrolimus capsules 1 mg, qm + 0.5 mg, qn, and Mycophenolate mofetil (MMF) 250 mg, qd).

Laboratory tests in clinic showed the following:

• The count of peripheral WBC was $2.49*10^9$/L, red blood cell was $2.98*10^{12}$/L, hemoglobin was 95 g/L, platelet was $86*10^9$/L, lymphocyte was $0.64*10^9$/L, and the level of serum creatinine was 138 μmol/L, and that of CRP was 31.25 mg/L. Peripheral leukocyte counts were below normal, especially lymphocyte count.

• Pulmonary CT on admission showed bilateral scattered flocculent fuzzy lesions (Figure 3D).

• Repeated COVID-19-specific RT-PCR on nasopharyngeal aspirate was again confirmed positive.

We treated him with oseltamivir, abidol, moxifloxacin, recombinant human interferon alpha (30 μg, qd), low-dose methylprednisolone (40 mg, qd), and human immunoglobulin for intravenous injection (IVIG) (10 g, qd), together with symptomatic supportive treatment (Figure 2). The patient's symptoms were alleviated gradually, and so were the inspection results. Pulmonary CT re-examination presented reduced flocculent fuzzy lesions; some were already fibrotic (Figure 3E).

However, results on March 2 showed that three series in peripheral blood decreased progressively:

• The count of peripheral WBC was $2.05*10^9$/L, lymphocyte was $0.5*10^9$/L, red blood cell was $1.24*10^{12}$/L, hemoglobin was 41g/L, platelet was $25*10^9$/L, and the level of serum CRP grew to 101.79 mg/L.

• The new COVID-19 test continued to be positive.

• However, the level of serum creatinine was lower (113.8 μmol/L).

MMF was suspended due to its potential bone marrow suppression, and only tacrolimus was still administered to maintain basal immunosuppression, at a concentration of around 2 ng/ml. Then we carried out a lymphocyte subset type test. After comprehensive treatments to control infection, a blood transfusion, and improvements in immunity, the pneumonia was alleviated, and the COVID-19 RT-PCR test was finally negative on March 20. Repeated tests after were still negative. Tacrolimus capsules was added to increase the concentration of FK506; it was kept around 4.5 ng/ml. However, there was no antibody produced until March 26. IgM and IgG all appeared positive. This patient successfully recovered from COVID-19 and showed no signs of rejection during this long hospital stay. He was discharged on March 28.

Discussion

SOT recipients with COVID-19 often present with mild or atypical symptoms [5] and fever may be absent [5]. In the first case, the patient only complained about abdominal discomfort and weakness during the first week after liver transplantation, without respiratory symptoms of COVID-19 such as dry cough [6–8]. It is difficult to consider the possibility of COVID-19 directly based on these complaints, particularly in winter, when respiratory viral activity is high, and cases of co-infection can easily cause misdiagnosis. Routine testing for COVID-19 was recommended during the outbreak.

Blood test indicators of the first patient showed that the level of transaminase rose rapidly in the early stage of hospitalization, and gradually decreased after reaching the first peak on January 21, which was a sign of early graft dysfunction. The absolute value of lymphocytes remained smaller than the lower limit of the normal reference since COVID-19 was diagnosed. With subsequent acute rejection, the markers of liver function fluctuated again, and so did the count of lymphocytes. In addition, there was a tendency of repeated fluctuations in the level of bilirubin index,

transaminase, and cytokines. These variations of laboratory data were not only related to the progression of COVID-19, but also related to the immune state.

Regarding the first case, temporary discontinuation of immunosuppressant allowed the patient an opportunity to reacquire anti-infection immunity, which is conducive to eliminating the virus, and daily use of low-dose methylprednisolone and IVIG also played an important role [9]. However, while the patient was healing from pneumonia, risk of acute rejection also increased. The impaired liver function of this patient indicated that the balance between infection, immunity, and rejection had been broken. The resumption of tacrolimus did not stop the acute rejection immediately. FK506 concentration of this patient was further retrospectively analyzed, and we found that the concentration was not maintained in a reasonable range. Furthermore, it was considered important to use appropriate doses of corticosteroids throughout the process, which could suppress inflammatory storms [10–12] and promote the recovery from pneumonia, without severe side effects [13]. When treating the second patient, although he has been diagnosed with COVID-19, we did not completely discontinue the immunosuppressant. Instead, we changed the immunosuppressive regimen to low-dose oral tacrolimus and MMF, kept the FK506 concentration within the lower range, and supplemented the regimen with low-dose methylprednisolone-maintenance treatment. The patient did not develop acute rejection at any point during the process, and the COVID-19 was also well controlled. However, severe bone marrow suppression developed during the process, and MMF was suspended and systemic supportive treatment was strengthened to promote the recovery of his hematopoietic function. However, there were also reports indicating that respiratory viral infections appear to be a risk factor for both acute and chronic rejection, with the greatest risk in lung transplant recipients, although data available on this topic are often conflicting [5] and the pathogenesis of the link between respiratory viral infections and rejection is not clearly understood. It's reported that for most patients, viral load in nasopharyngeal samples from patients with COVID-19 peaked within the first few days after symptom onset before declining, and median duration of viral shedding from first to last positive test was 12 days [14]. What's more, most patients had an antibody response at 10 days or later after onset of symptoms [15]. But in these two SOT recipients, the viral RNA remained positive for a longer period of time and antibody response was much later, this phenomenon may be related to their immunosuppressed state, which needs further study.

In conclusion, the clinical features and management of two COVID-19 cases in SOT recipients were reported above. From this experience, the regimen for COVID-19 positive SOT recipients should be adjusted after comprehensive evaluation, according to the infection level, immunosuppressant concentration, immune status, and side effects. A therapeutic regimen consisting of reduction of calcineurin inhibitors and MMF, combined with low-dose methylprednisolone, is recommended at present. Certainly, further data are needed to gain better understanding of the impact of immunosuppressive therapy on the clinical presentation, severity, and outcome of COVID-19 in SOT recipients.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation. The transplantations were performed according to the Declaration of Istanbul, and no executed prisoners were used as donors.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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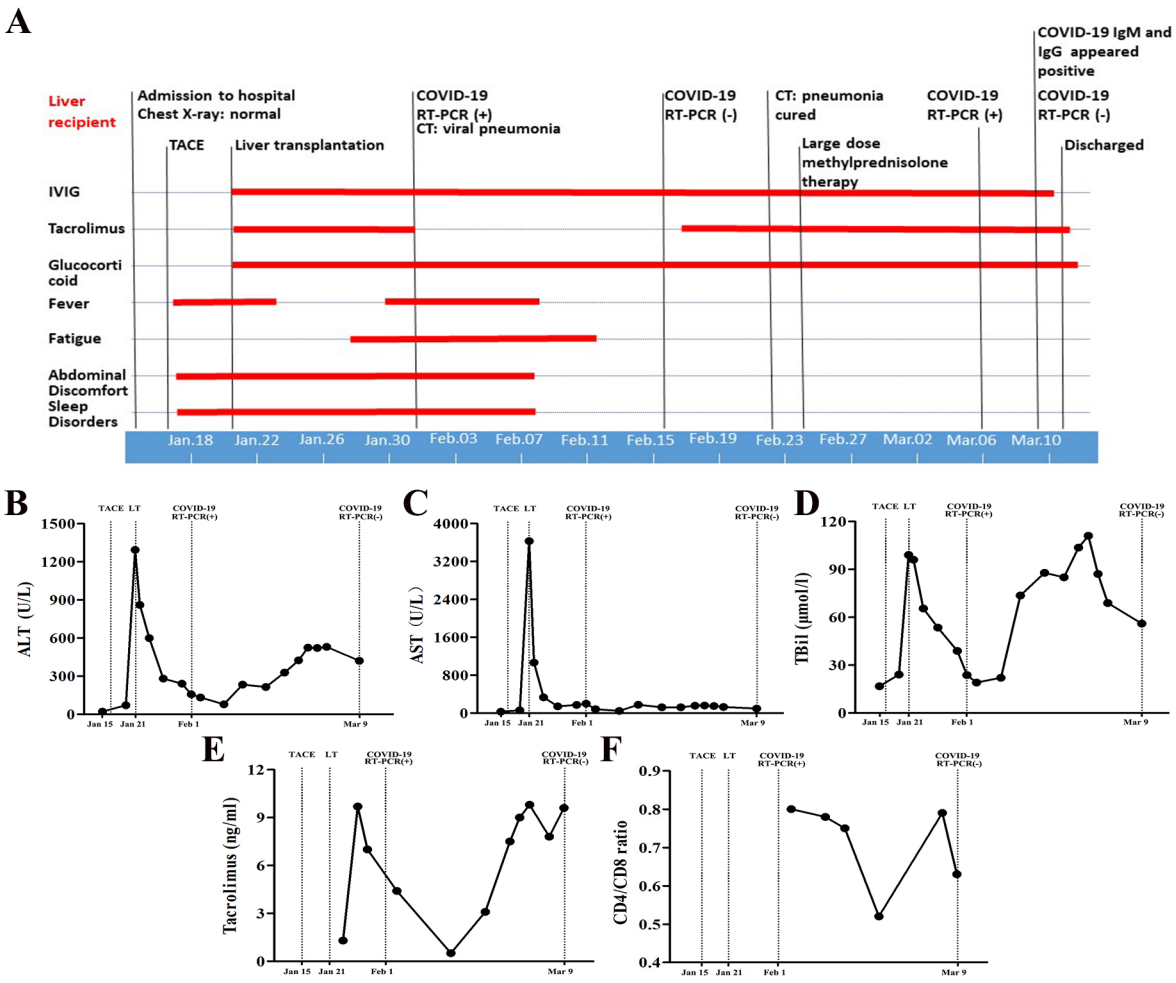
Figure 1. The timeline of clinical diagnosis and treatment of the COVID-19-positive liver transplant recipient during hospitalization (A), and changes of his liver function and immune status in the meantime (B-F).

Figure 2. The timeline of clinical diagnosis and treatment of the COVID-19-positive kidney transplant recipient during hospitalization (A), and changes of his renal function and immunosuppressant concentration in the meantime (B-C).

Figure 3. Changes in chest CT scan of these two COVID-19-positive SOT recipients during hospitalization. A-C: pulmonary imaging of liver transplant recipient; D-F: pulmonary imaging of renal transplant recipient.



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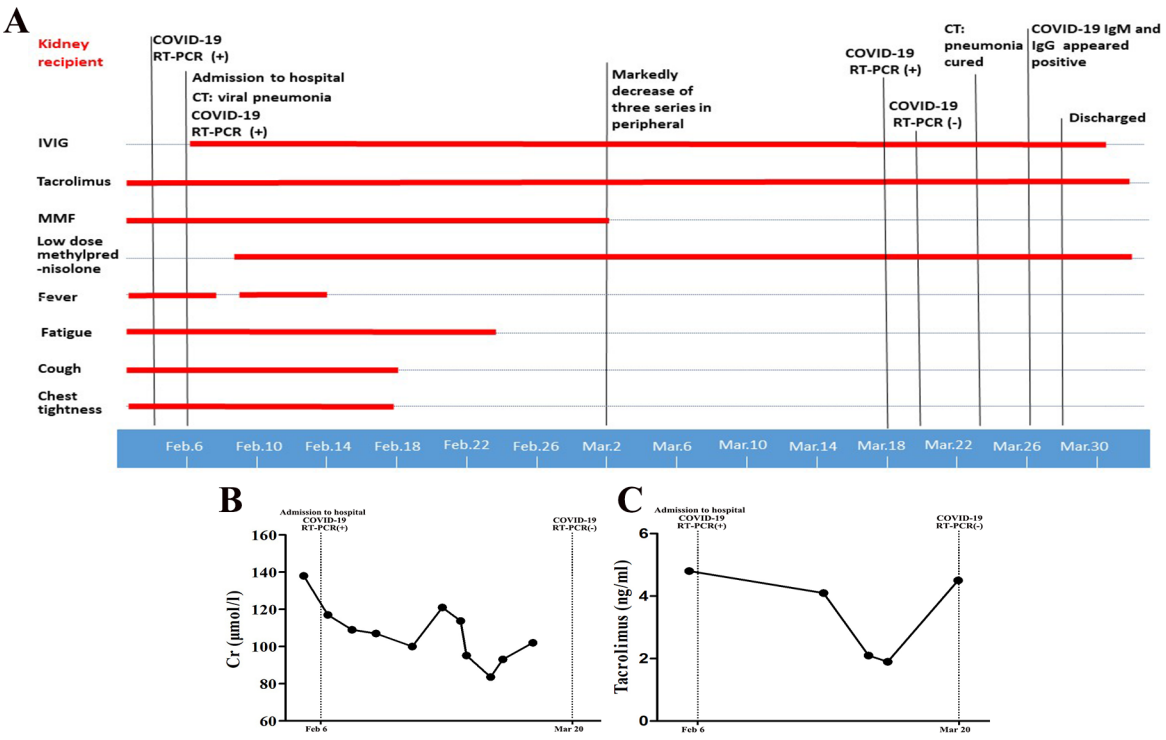

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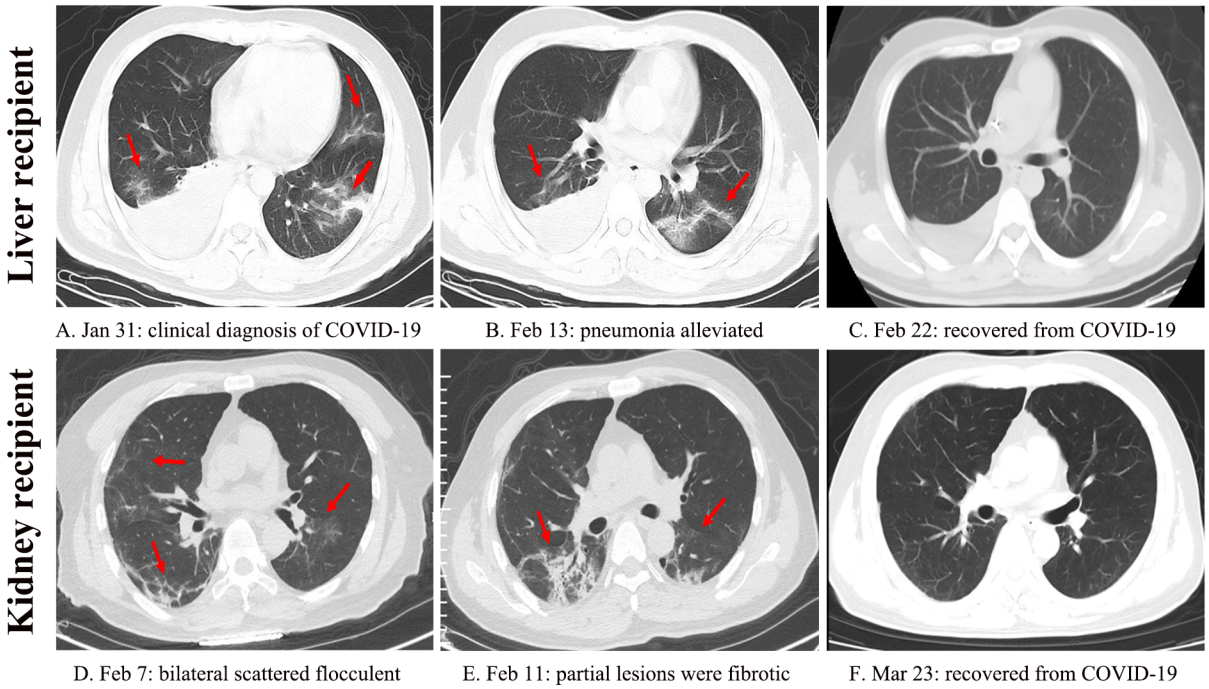

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