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Case Report

Novel Coronavirus (SARS-CoV-2) Pneumonia in a Renal Transplant Recipient: Case Report

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Abstract

A pandemia is threatening public health he worldwide due to novel corona virus disease which was first reported in Wuhan, China at the last days of December 2019. Clinical manifestations of SARS-CoV-2 vary among people. Patients with diabetes mellitus, hypertension and cardiovascular disease, chronic renal disease and malignancy especially have risk of developing severe disease. Kidney transplant recipients also might have an increased risk for infection. We present a case of 68 years old male patient who has been renal transplantation and diagnosed covid 19 pneumonia. Hydroxychloroquine, oseltemavir, azithromycin, enoxaparin and oxygen were started for pnemonia. Immunosuppressive therapy [tacrolimus, methylprednisolone, Mycopholate Mofetil (MMF)] maintained constant except MMF. During the follow up immunosuppressant blood levels increased to 40 ng/dl and he was left with steroid therapy. He was recovered completely and his CNI blood levels returned to standard range. In this case we intend to underline difficulties in treatment and follow up of renal transplant patients infected by SARS-CoV-2 and also need for updated treatment guideline.

Keywords: SARS-CoV-2; Pneumonia; Renal transplantation; CNIs

Introduction

In December 2019, a novel coronavirus strain named SARS-CoV-2 (formerly called 2019-nCoV) disease outbreak occurred in Wuhan, Hubei Province, China, and rapidly spread to the rare as worldwide and the infection was accepted by the WHO as a pandemic [1]. Clinical manifestations of SARS-CoV-2 infection varies among people, ranging from asymptomatic carrier state to severe rapidly fatal pneumonia [1,2]. SARS-CoV-2 has been associated with severe morbidity and mortality in elderly patients, diabetes mellitus, hypertension, chronic kidney disease and complicated with cardiovascular or pulmonary comorbidities and in immune incompetent populations [3]. Furthermore, kidney transplant recipients also might have an increased risk for infection.

Because specific drugs to treat SARS-CoV-2 have not yet been revealed. Antiviral therapy for SARS-CoV-2 and immunosuppressive treatment have to continue concomitantly for preserve their renal functions. Identify optimal therapy for this population is significant. Clinical information of COVID-19 on solid organ transplant recipients and the effect of the immunosuppression regimens on the clinical course of COVID-19 are still lacking [4-6]. We need further cases for specify an optimal immunosuppressive treatment for kidney transplant recipients. In this case we report a male kidney transplant recipient diagnosed COVID-19 pneumonia, who was maintained reduced immunosuppressive medication with treatment for COVID-19.

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Case Report

A 68 years old male patient received kidney transplant 5 months ago from a live donor. He had been treated for diabetes mellitus and hypertension for 20 years. He was admitted to emergency room on 31st March 2020 with cough and dyspnea. He had the symptoms for one week. He had no fever or myalgia. He didn't have a history of trip to a foreign country or exposure to any confirmed COVID-19 case. His routine immunosuppressive regimen consisted of Mycophenolate Mofetil (MMF) 2000 mg per day, tacrolimus 2 mg per day, and methylprednisolone 8 mg daily. Also, he had been treated with insulin for diabetes and doksazosin, amlodipine and carvedilol for hypertension. His serum creatinine levels stabilized between 1.1 mg/dL - 1.3 mg/dL since the transplantation.

On admission he had body temperature of 36.7°C and his blood pressure was 150/70 mmHg. He had a pulse of 83 and respiratory rate of 22 per minute and oxygen saturation of 92% under 2 liters of oxygen therapy. His laboratory results revealed a White Blood Cell count (WBC) 3830 uL, lymphocytes 380 uL, lactate dehydrogenase 247U/L, ferritin 228 ng/mL, fibrinogen 920 mg/dL, D-Dimer 1421 ng/mL, creatinine 1.18 mg/dL and eGFR 63 mL/minute/day. C-reactive protein was 9.7 mg/dL, Procalcitonin level was <0.05 (negative). Tacrolimus level was 6.5 ng/dL chest CT showed bilateral wide spread ground-glass opacification which was typical for viral pneumonia and also bilateral consolidation in lower lobes (Figure 1). PCR test for covid 19 resulted positive (Table 1).

Hydroxychloroquine 400 mg/day, oseltemavir 150 mg/day, azithromycin 250 mg/day, enoxaparin 4000 units/day and 2 liters of nasal oxygen were started immediately. MMF dose reduced to 1000 mg from 2000 mg per day. Tacrolimus corticosteroid dosages remained unchanged. On the second day of his hospitalization his saturation of oxygen decreased to 89% while he was administering 2 liters of nasal oxygen, CRP raised up to 24.9 mg/dL and he was transferred to intensive care unit. Favipiravir therapy started with piperacilin/tazobactam. Hydroxychloroquine and azithromycin ended up in five days.

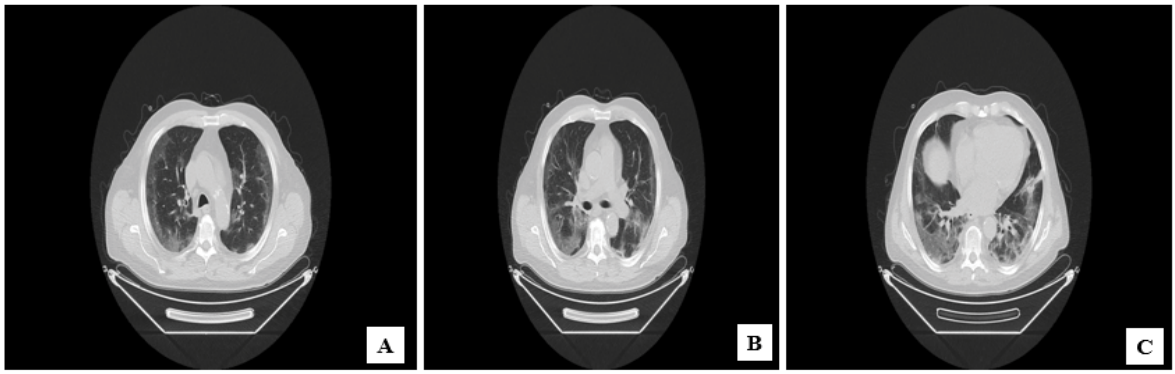

Figure 1: Images shown are chest high-resolution computed tomography obtained on first day (A), day7 (B), day 12 (C) of illness.

Table 1: Clinical laboratory results.

Parameters	31.03.2020	12.04.2020	24.04.2020
White Blood Cell (x10^3/uL)	3.83	8.1	7.01
Lymphocyte (x10^3/uL)	0.38	0.59	1
Hemoglobin (g/dL)	12.4	11.2	11.3
Platelet (x10^3/uL)	248	502	270
Creatinine (mg/dL)	1.18	1.19	1.24
AST (u/L)	24	26	13
ALT (u/L)	15	34	19
Albumin (g/L)	37	30.9	34
LDH (u/L)	247	269	251
C-RP(mg/dL)	9.7	24.9	2.7
Procalcitonin (ng/mL)	4.5	49.5	0.12
D-Dimer (ng/dL)	1421	1330	745.15
Fibrinogene (mg/dL)	920	735	617
Ferritin (ng/dL)	228	367.9	213.7

On 12th day tacrolimus blood level resulted 43 ng/dL although tacrolimus dosages were constant during his hospitalization. The next day we repeated blood level test and it ended up 20 ng/dL, so that tacrolimus and MMF were discontinued because of excessive immunosuppression. The patient's clinical condition was stable, he had no diarrhea, he was normovolemic. He didn't receive any other drugs or dietary supplementation that inhibit cytochrome P450 3A and cause an elevation in blood level of tacrolimus in his medication. The patient's renal functions consisted between normal ranges. After 10 days of discountation of immunosuppression tacrolimus blood level decreased to 10 ng/dL and 0.5 mg per day oral tacrolimus has started again (Figure 2). During these 10 days patient's inflammatory markers and symptoms decreased and COVID-19 therapy ended. He was completely recovered and discharged from hospital. He is still following up by nephrology outpatient clinics.

Discussion

COVID-19 infection which is declared pandemic by WHO, firstly reported at the end of December 2019 in Wuhan, China is still being a worldwide threaten for public health [1]. Patients suffer from hypertension, diabetes and cardiovascular disease have high risk for infection and severe disease. Kidney transplant recipients have significantly suppressed immune response so this population, also, has advanced risk for infection. Their symptoms may be various, ranging from asymptomatic carrier state to severe rapidly fatal pneumonia, so that diagnose and treatment needs careful consideration [1,2].

Specific drugs to treat SARS-CoV-2 will take several years to develop and evaluate. Therefore, a viral RNA polymerase inhibitors favipiravir, a broad-spectrum antiviral drug that interferes with the viral replication, were initiated based on Novel Coronavirus Pneumonia Diagnosis and Treatment Plan [6]. Long-term administration of immunosuppression in solid organ transplant recipients may increase the risk of infection, though there is no clinical evidence for an increased morbidity/mortality in respiratory tract infections caused by respiratory viruses such as the known group of coronaviruses so far (with exception of SARS and Middle East Respiratory Syndrome coronavirus [MERS]) [6]. Management of immunosuppression therapy of these patients is challenging, and it should be modified according to patient's age, time of transplantation, comorbid diseases and severity of the infection.

Most drug interaction concerns with favipiravir are of minimal or uncertain clinical significance. Favipiravir is metabolized by aldehyde oxidase and also inhibits this enzyme, but there are no known clinically significant drug interactions involving this mechanism. Favipiravir is

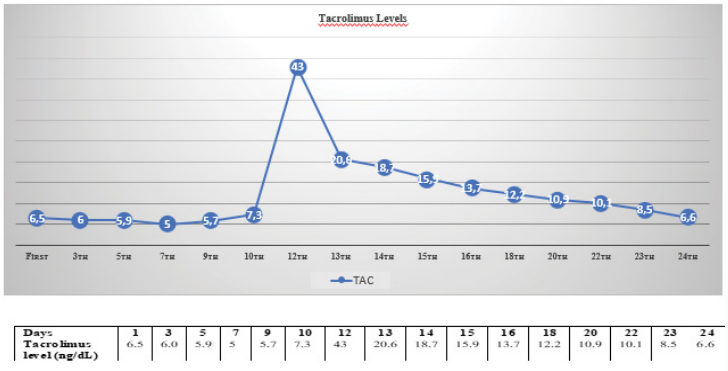

Figure 2: Blood tacrolimus concentrations during follow-up.

also a weak CYP2C8 inhibitor, but this is unlikely to result in many clinically significant interactions [7]. However, there is no evidence that favipiravir interacts with tacrolimus *via.* this way.

Zhu et al. [9] reported a case about kidney transplant recipient who was diagnosed COVID-19 pneumonia and fully recovered with intravenous immunoglobulin, biapenem and methylprednisolone 4 mg per day. His immunosuppressive drugs had been discontinued during this therapy. The patient's symptoms were severe and they used methylprednisolone for anti-inflammatory and graft protective effects. They claimed that although the patient recovered completely, single case couldn't be a reference and more evidence based dates were needed to be shared to determine an optimal therapy for this population.

Systemic inflammatory response plays most important role in the course of the infection. It may lead to poor respiratory outcome and ARDS (9-11). Shie et al. suggest two phases of the COVID-19 infection. In the first phase viral replication activates immune response and immune system could achieve viral clearance in this phase. In the second phase when severe disease is occurred increased inflammation causes respiratory system damage [10]. Since the severity of COVID-19 disease is based on high proinflammatory condition, some authors suggest that transplant recipients may benefit from the long term immunosuppression which may protect them from cytokine storm [11]. Kidney transplant recipients with COVID-19 disease also may present with mild clinical signs without fever and respiratory symptoms. Seminari et al. [12] reported a renal transplant patient with mild symptoms and recovered completely who maintained his immunosuppressive therapy without hydroxychloroquine or dopinavir/ritanavir because of drug reactions. Maintaining the optimal drug level of calcineurin inhibitors is another important issue during the follow-up of these patients. Dopinavir/ritanavir competitively inhibits cytochrome p450 activity that results high blood level of CNI which may cause serious adverse effects and difficulties in treatment of the infection [12,13].

In our case we present a kidney transplant patient with coronavirus disease who had high tacrolimus blood level during the therapy. Although increased drug levels his renal functions were stable and he didn't have any adverse effects of high tacrolimus blood saturation. We couldn't define the exact cause of raised blood levels since do pinavir/ritanavir wasn't in our medication protocol.

In conclusion we report COVID-19 in a renal transplant recipient successfully treated with favipiravir and we intend to underline difficulties in treatment and follow up of renal transplant patients infected by coronavirus 2019. Maintenance treatment with corticosteroids was continued as well since no negative impact was found. The present findings in our case suggest that COVID-19-related inflammatory process increases the level of tacrolimus, so blood tacrolimus level should be monitored regularly, drug dosage reduction or discontinuation may be required if necessary. Also we want to emphasize the need of actual guidelines for management of COVID-19 disease in renal transplant recipients.

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Conflict of Interest statement

There are no conflicts of interest in connection with this paper.

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Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Guarantors

Dede Sit, Hasan Kayabasi, Ezgi Ersoy Yesil

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