

Manuscript name: How We Treated a Kidney Transplant Recipient Who Was Receiving Sirolimus During the SARS-CoV-2 Pandemic? *Primum Non Nocere.*

SARS-CoV-2 Salgını Sırasında Sirolimus Alan Böbrek Nakli Alıcısını Nasıl Tedavi Ettik? İlk Önce Zarar Verme

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Abstract

The new Coronavirus SARS-CoV-2 (COVID-19) epidemic continues to affect the world. It is emphasized that COVID-19 is more severe in patients with solid organ transplantation, and the risk of mortality may be higher than in the normal population. Herein, with the first time, we described a COVID-19 pneumoniae kidney recipient case treated with sirolimus. A 49-year-old male patient had kidney transplantation 13 years ago. He was used prednisolone and sirolimus. His main complaints were fever (38.3°C) and weakness. Atypical pneumoniae was diagnosed with thorax computed tomography. The respiratory specimen of the patient was positive with COVID-19 by PCR test. Sirolimus was stopped due to the immunosuppressive effect, and the treatment switched to low dose everolimus. Also, hydroxychloroquine, oseltamivir and azithromycin triple therapy was started for five days. The patient was discharged with healing on the seventh day.

Keywords COVID-19; Kidney transplantation; Sirolimus

Öz

Yeni Koronavirüs SARS-CoV-2 (COVID-19) salgını dünyayı etkilemeye devam etmektedir. Organ nakli yapılan hastalarda COVID-19'un daha şiddetli olduğu ve ölüm riskinin normal popülasyona göre daha yüksek olabileceği vurgulanmaktadır. Burada ilk kez; sirolimus ile tedavi edilen COVID-19 pnömonisi geçiren böbrek nakilli bir hastayı sunmayı amaçladık. On üç yıl önce böbrek nakli olan 49 yaşında erkek hasta 38.3°C ateş ve halsizlik şikayeti ile başvurdu. İmmünesupresif ilaç olarak prednisolon ve sirolimus kullanmakta olan hastanın toraks tomografisinde atipik pnömoni tanısı koyulup COVID-19 PCR testi pozitif saptandı. İmmünesupretif etki nedeniyle sirolimus kesilerek everolimus tedavisine geçildi. Ayrıca hidroklorokin, oseltamivir ve azitromisin üçlü tedavisine beş gün süreyle başlandı. Hasta yedinci günde iyileşerek taburcu edildi.

Anahtar Kelimeler COVID-19; Böbrek transplantasyonu; Sirolimus

INTRODUCTION

The new Coronavirus SARS-CoV-2 (COVID-19) epidemic that started in China-Yuhan since December 2019 continues to affect the world.¹ The number of people affected by COVID-19 in the world has exceeded 9 million people. With age, the risk of mortality was higher in patients with the comorbid disease, especially diabetes mellitus and hypertension.² There is no clear guidance on immunosuppressive management of kidney transplant patients with COVID-19 positive pneumoniae.³ Presentations of patients with COVID-19 pneumoniae in case reports, as in the healthy population, have been recommended to continue steroid maintenance therapy, withdrawn or reduce mycophenolate mofetil (MMF) and calcineurin inhibitors (CNI).^{4,5} In many solid organ transplant patients, it has been reported that non-infectious pneumonitis due to the use of mammalian target of rapamycin inhibitors (mTORi) - especially more sirolimus - has developed, and a significant improvement in pneumoniae findings has been noted with discontinuation of the drug.^{6,7} It is very difficult to distinguish since both sirolimus and COVID-19 associated pneumoniae make infiltration and ground glass appearance in the interstitium. To our knowledge, there is no information about this condition that has not been published in the literature yet. First time with this case, we aimed to present a COVID-19 pneumoniae in a kidney transplant recipient who treated with sirolimus.

CASE REPORT

49-year-old male patient had a kidney transplant 13 years ago from his 66-year old mother. Before transplantation, he was on chronic hemodialysis program 3 days/week for 2 years due to chronic pyelonephritis. Firstly; informed consent form was signed from the patient. His main complaint was; fever (38.3°C) and weakness. He did not have clear respiratory symptoms such as dry cough, shortness of breath or acute gastroenteritis. The nasopharyngeal COVID-19 PCR swab was positive. For PCR test; after the acceptance of the samples in the microbiology laboratory, the samples were taken to the level 3 biosafety negative

pressure room. RNA isolation from nasopharyngeal swab sample was performed with the EZ1 (Qiagen, Germany) device. Elution of 60 µl of 400 µl sample was taken and used as a template in RT-PCR reaction. At the end of the reaction, Cycle Threshold (CT) values were used as an approximate indicator of the number of copies of the SARS-CoV-2 RNA. A CT value of less than 45 was interpreted as positive for the SARS-CoV-2 RNA. As vital signs; blood pressure 114/80 mmHg, cardiac pulse: 75/min, respiratory rate: 22/min, oxygen saturation 95% detected in the air room. As a result of thoracic computed tomography (CT), the patient was admitted to the hospital because of the bilateral, frosted glass image that spread from the periphery to the center (Figure-1).



Figure 1: Telecardiogram image of the patient

The patient who was using prednisolone 5 mg and 1mg sirolimus maintenance therapy switched to low dose everolimus 2x0.25 mg/day in order not to confuse sirolimus-associated non-infectious pneumonitis. In terms of basal graft function, serum creatinine level was 2.6 mg/dl. hydroxychloroquine, oseltamivir and azithromycin triple therapy was given for five days according to estimated glomerular filtration rate (e-GFR). The patient's oxygen requirement from 2 liters lasted 2 days from hospitalization.

on. Then, oxygen saturations started to be around 97% in the air room. The vital findings and laboratory parameters observed in the daily follow-up of the patient are shown (Table-1). The patient was discharged on the seventh day with healing.

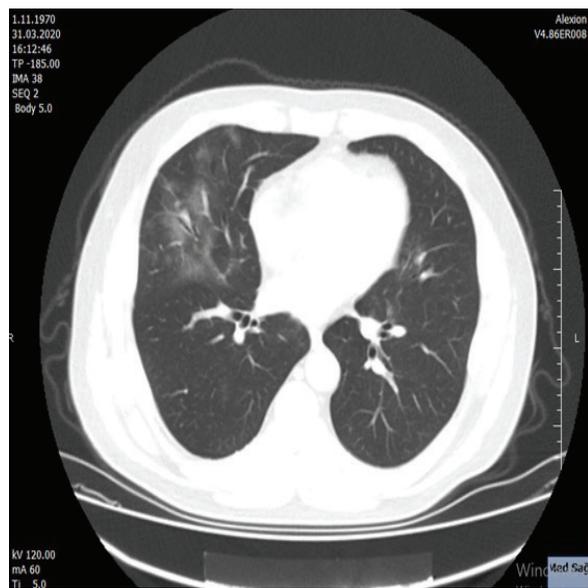


Figure 2: Thorax CT image at the first presentation of the patient

Table-1: Laboratuar parameters of patient's follow up			
Parameter	Day 0	Day 3	Day 7
Blood Pressure (mmhg)	115/75	120/77	125/75
Heart Rate (number/minute)	77	82	78
Oxygen saturation in air room	95	97	97
Fever (C0)	38,3	36,7	36,1
ProtrombinTime	20,5	22,5	23,7
D-Dimer (ug/FEU/ml)	403	456	336
Ferritin (mg/l)	281	181	197
C-Reactive Protein (mg/dl)	20	13	3
Procalcitonin (ng/ml)	0,12	0,11	0,10
WBC(K/ul)	3,86	3,76	5,75
Hemoglobin (g/dl)	12	11,3	11,9
Lymphocyte/Neutrophil ratio	1,03/2,42	1,08/2,3	1,45/3,86
Platelet (K/ul)	117	134	285
Serum Creatinine (mg/dl)	2,66	2,67	2,72
AST /ALT(U/L)	22/15	12/13	17/19
WBC: Wight blood count, AST: Aspartaminotransferaz, ALT: AlaninAm-inotransferaz			

DISCUSSION

In literature, there is still no evidence-based information on how to monitorize patients with COVID-19 positive kidney transplants and reduce or discontinue immunosuppressive drug doses.^{4,5} The patient was using steroids and sirolimus due to various side effects of MMF and CNI in the early posttransplant period. Therefore, sirolimus switched to low-dose everolimus as sirolimus related interstitial pneumoniae was emphasized in many publications, whereas fewer cases were reported in kidney transplant patients receiving everolimus. In a retrospective study; sirolimus induced pneumonitis was detected in 16.7% of kidney transplant patients. The most frequent symptom was fever, which seen in 9 (75%) patients, followed by dyspnea and cough.⁸ Because of pandemic conditions in our country, both sirolimus and COVID-19 related atypical pneumonitis findings can be seen similar; the patient was evaluated as COVID-19 pneumonitis and treated by triple antivirals for five days.⁹ However, drug-induced non-infectious pneumonitis improved symptoms after withdrawal of the sirolimus, and as bronchoscopy is a very invasive procedure for screening of atypical infection and COVID-19 transmission risk is very high, we did not apply bronchoalveolar lavage (BAL). Our patient had a 13-year kidney transplant and had hypertension and chronic allograft nephropathy. Due to these comorbid conditions, daily 5 mg maintenance steroid and low dose everolimus protocol were adopted. He was discharged on the seventh day of hospitalization without any acute graft dysfunction or respiratory failure. In summary, in the management of COVID-19 pneumoniae developing in kidney transplant patient who use mTORi, we suggest along with the discontinuation of the sirolimus, if appropriate, maintenance steroid, low-dose CNI or low-dose everolimus treatment protocol may be appropriate. We think that this approach may has to confirm with randomized and controlled trials.

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