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First Experience in Management of Coronavirus Disease 2019 (COVID-19) in Kidney Transplant Patient – Case Report

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Abstract

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has recently emerged in the world. There are limited data describing the clinical progression of COVID-19 in transplanted patients. In the general population, clinical presentation ranges from asymptomatic infection to severe pneumonia and may also develop renal failure. In kidney transplant (KT) patients, management of these patients was mainly based on anecdotal experience.

CASE REPORT: We report our first experience of KT patients with COVID-19. A 49-year-old male with KT in 2017 presented on March 20, 2020, with fever, weakness, smell loss, chest pain, and caught. On chest X-ray, he presented ground-glass opacities and bilateral pneumonia. There was a slight progression to acute hypoxic respiratory failure. We reduced immunosuppression therapy and since we suspected seasonal flu, we applied available antiviral oseltamivir till confirmation of RNA sequence of the SARS-CoV-2 virus. Moreover, we applied azithromycin and broad spectrum of antibiotics as well as an anticoagulant therapy. Graft function remained stable during 14 days of hospitalization. The patient clinically improved with decreasing oxygen requirements and manifested clinical recovery. After two negative PCR test, he was discharged and immunosuppression therapy was returned to previous.

CONCLUSION: This case highlights the importance of earlier outpatient hospitalization and testing which may improve COVID-19 outcomes among transplanted patients.

Introduction

In December 2019, in Wuhan, China, a new disease appeared that caused severe pneumonia and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was detected as a causative agent. Disease was called coronavirus disease 2019 (COVID-19). It was spread very fast to all continents, and on March 11, 2020, the World Health Organization (WHO) declared a pandemic [1]. It has been shown that virus was transmitted from person to person during unprotected contact, respiratory droplet, fecal-oral transmission, and vertical transmission from mother to child [2]. Moreover, it was shown that it uses ACE 2 receptors to enter the cell, similar to SARS-CoV. The clinical presentation is very diverse, from asymptomatic, mild, and moderate to severe [3].

Patients with transplanted kidneys are on continuous immunosuppressive therapy. Previous experiences with SARS and MERS have described deteriorating graft function in infections, even with a fatal outcome [4], [5]. At the root of dealing with them, as well as in all infections, is actually timely modifications or discontinuation of immunosuppressive therapy, except for corticosteroids according to the recommendations and appropriate specific therapy [6], [7]. It has been reported that in KT patients with COVID-19, it is necessary to modify the immunosuppressive therapy; unfortunately, there is a lack of reports about appropriate specific therapy for SARS-CoV-2 in KT patients [8], [9], [10].

First imported case of COVID-19 was detected in our country on February 21, 2020, and until May 15, 2020, there were a total number of 1723 patients, 1235 cured, including 1 KT patient and 7 patients on dialysis [11].

Case Report

We present here our first experience with COVID-19 in a 49-year-old male kidney transplant patient. He was transplanted 3 years ago, and the donor was his brother. Treated according to a protocol with four immunosuppressive therapies, Basiliximab as induction therapy and triple immunosuppressive maintenance

therapy that included corticosteroids, cyclosporine A (Cy A), and mycophenolic acid (MMF). From comorbidities present arterial hypertension, regulated by the following antihypertensive oral therapy: Calcium antagonist (nifedipine R a 20 mg 3 × 1), angiotensin II receptor blocker (ARB) losartan a 50 mg 2 × 1 and carvedilol a 6.25 mg 2 × 1, and obesity with body mass index (BMI) = 37.7. The patient regularly came for regular follow-up. No signs of transplant rejection were recorded during follow-up. Kidney function was stable, with values for serum creatinine of 110 μmol/L and calculated GFR of 109 ml/min, on the last control on March 3, 2020. The patient was given to sign a written consent.

On March 20, 2020, the patient experienced the first symptoms such as weakness, pain in the knees and hips, temperature up to 38.5°C, loss of taste and smell, and chest pain. According to the protocols of our Ministry of Health, the patient called the epidemiological services. Because the patient had a negative epidemiological history, he was referred to his general doctor with suspicion of seasonal flu. Oral treatment with ciprofloxacin a 500 mg 2 ° 1 and oseltamivir a 75 mg 2 × 1 (Tamiflu) was started immediately. The dose of cyclosporine A (Cy A) and MMF was reduced by 50% of baseline.

The temperature persisted and a persistent dry cough appeared, indicating that the patient needs to be tested. On March 23, 2020, a diagnosis of COVID 19 was made by proving the presence of an RNA sequence of the SARS-CoV-2 virus in the material from the nasal and throat swab. The same day, the patient was hospitalized at the University Clinic for Infectious diseases and febrile conditions.

At the time of admission, the patient was febrile 38°C and the physical status was positive. The auscultatory chest findings were in favor of sharper vesicular breathing.

The initial laboratory test showed an orderly leukocyte count, but a reduced lymphocyte count slightly elevated C reactive protein (CRP) and creatinine kinase (CK). The graft function was normal, but values for serum potassium were close to the lower limit. The hemostasis finding indicated lower platelet counts and a slight increase in d-dimers (Tables 1 and 2). The chest X-ray showed bilateral pneumonia (Figure 1).

The immunosuppressive therapy Cy A and MMF were discontinued and oral decortin a 15 mg were given as maintenance therapy. The ARB was interrupted. The rest of the therapy consisted of intravenous ceftriaxone a 2g 2 × 1, azithromycin a 500 mg 1 × 1, paracetamol when needed, subcutaneous clexane, and other oral supportive therapy such as Vitamin C, probiotics, potassium supplements, and hepatoprotectants (Table 3).

The patient after 9 days was afebrile. Of all the other symptoms, the dry cough lasted longer (Table 4). Regarding the laboratory findings, there has been a continuous improvement in the number of lymphocytes, platelets, as well as serum values for CRP and CC. A moderate increase in d-dimers and moderate transaminase activity also has been observed (Tables 1 and 2). The graft function remained stable with serum creatinine 97 μmoll/L.

Table 1: Biochemical findings during hospitalization

???	March 24	March 28	April 02	April 04
Hb g/L	141	140	136	138
RBC 10^12/L	4.6	4.7	4.6	4.6
WBC 10^9/L	4.4	7.5	7.4	5.8
PLT 10^9/L	123	166	264	259
Htc rv	0.40	0.39	0.38	0.40
Ne 10^9/L	0.84	0.87	0.67	0.63
Ly 10^9/L	0.08	0.07	0.16	0.20
Mo %	0.08	0.06	0.15	0.15
Eo %			0,02	0,02
Glucose mmoll/L	5.3	6.9	5.0	5.2
Urea mmoll/L	7,0	4,0	3,9	4,4
Creatinine/μmoll/L	100	102	104	97
Tot.bil μmoll/L	11			
Dir/ind μmoll/L	3/8			
ALT U/L	41		88	80
AST U/L	36		54	38
LDH U/L	161	334	316	244
CK U/L	239	231	93	
CK-MB U/L	14	17		
GGT U/L				23
Troponin ng/ml	34.6			
K mmoll/L	3.6	3.0	2.9	3.3
Na mmoll/L	138	133	138	138
Ca mmoll/L	2.2	2.2	2.16	2.2
Total proteins g/L	65			
Globulins g/L	29			
Albumins g/L	36			
CRP mg/L	45	87	30	6

Hb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, PLT: Platelet, Ne: Neutrophils, Ly: Lymphocytes, Mo: Monocytes, Eo: Eosinophils, Tot.bil: Total bilirubin, dir/ind: Direct/indirect, ALT: Alanine Transaminase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase, CK-MB creatine kinase: MB, GGT: Gamma-glutamyl transferase, K: Kalium, Na: Sodium, Ca: Calcium, CRP: C Reactive protein

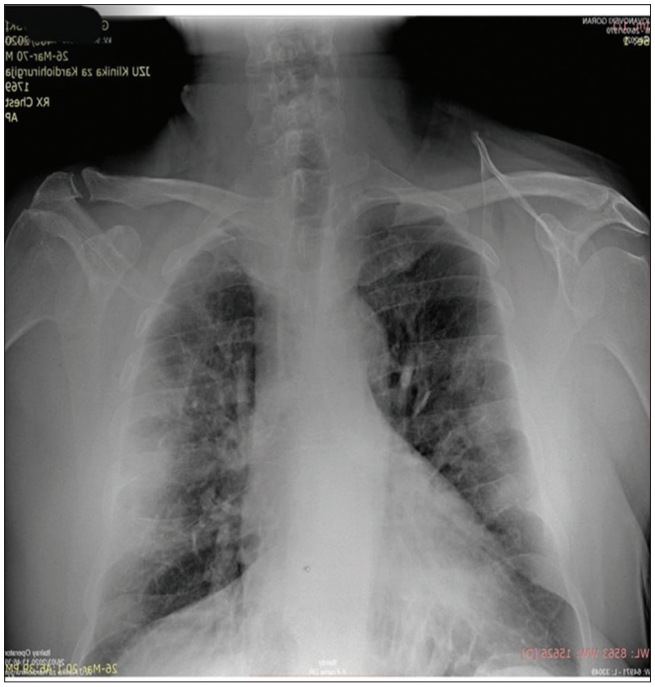

Figure 1: Bilateral pneumonia (chest X-ray on the 3th day)

After 15 days of hospitalization and two consecutive negative nasal and throat swab tests for SARS-CoV-2, the patient was discharged. After discharge, the Cy A and MMT therapy were restarted, gradually within 7 days to previous maintenance dosage. On the first control 12 days after hospitalization, renal function was unchanged and chest X-ray picture finding showed resolving of pneumonia (Figure 2).

Table 2: Hemostasis findings during hospitalization

Date	PLT 10^9/L	Hematocrit	Prothrombin time (s) (9.8–14.2)	Activated partial (s) (27.9–29.1)	Thrombin time (s) (16.1–19.01)	d-dimers (0–500)
March, 24	111	41.3	10.2	29.1	17.2	581
April, 05	253	39.9	10.36	25.5	19.01	1004

Table 3: Duration of clinical signs and symptoms

	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Temperature	38.0	38.4	38.3	37.4	38.5	36.4	38.3	38.6	38.5	37.3	37.2	37.5	37.5	37.5	37.1	37.1	36.6	36.8	36.6
Fever																			
Dry cough																			
Chest pain																			
Pain in the knees and hips																			
Loss of taste and smell																			
SpO_2 %					92	90	91	86	92		91	95	96	95	97	97	95		

Table 4: Therapeutic approach before and during the hospitalization

Therapy/days	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Decortin mg	5	5	5	5	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
MMF 1 g/day																			
Cy A 50 WWmg/day																			
Caps. Oseltamivir a 75 mg 2 × 1																			
Tab. Ciprofloxacin a 500 mg 2 × 1																			
Amp. Ceftriaxon a 2 g/day																			
Amp. Azitromycin a 500 mg/day																			

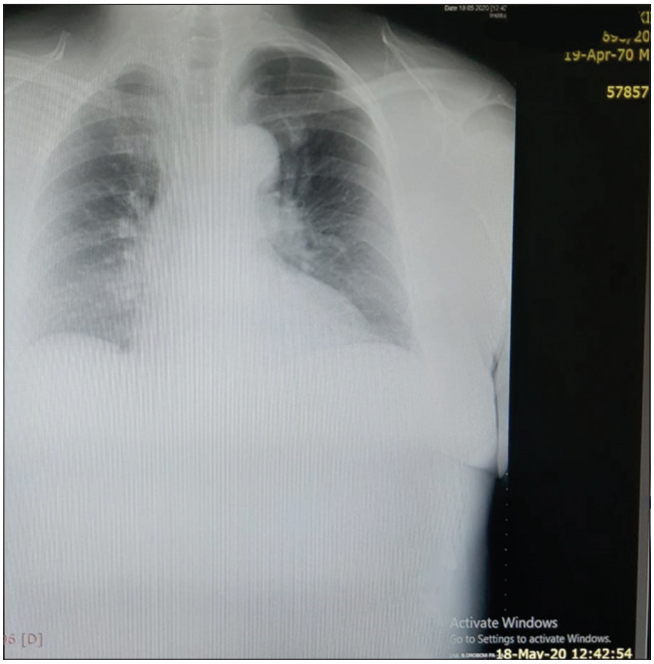

Figure 2: Findings resolved (chest X-ray after 24 days)

Discussion

From the current findings, the biggest risk of becoming infected with COVID-19 disease is through contact with a person with respiratory disease, but the fact that we have a patient with a negative epidemiological survey indicates that the spread of infection by asymptomatic carriers is also important [12]. In terms of gender and age, it has been reported that men and advanced age play a role in the severity of clinical presentation and mortality [13].

Patients with a KT are undergoing permanent immunosuppressive therapy, which causes a state of immunocompromised and often consequently, the infective diseases can have a changed clinical picture. In our first case, the clinical manifestations were fever, high temperature, dry cough, malaise, joint pain, and loss of sense of smell and taste, symptoms identical to those of the general population[2].

Clinical presentation may vary from asymptomatic to severe needing respiratory support. The presence of other comorbidities and conditions, such as high blood pressure, diabetes mellitus, chronic heart disease, chronic respiratory disease, and obesity, has been described as risk factors not only for the onset of COVID-19 but also for the progression and severity of clinical presentation. In our case, the patient was also overweight and had high blood pressure, which was probably the reason for the presentation of moderate to severe clinical picture, but without the need for oxygen support or respirator [14], [15].

Long-term use of immunosuppressive therapy is a reason to reduce T lymphocytes and reduce immunity in patients with transplanted organs. Therefore, modification or total cessation of immunosuppressive therapy, especially of MMF and Cy A, is extremely important in all infections but also in COVID-19 [6], [9]. In our case, the patient was on triple maintenance therapy: Corticosteroids, MMF, and Cy A. During the first three days, the dose of MMF and Cy A was reduced by 50%, and on the day of hospitalization they were discontinued. Table decortin 15 mg/day was established as maintenance therapy. Although experience has suggested that the MMF and calcineurin inhibitor should be discontinued, there are some studies that suggest that Cy A inhibits the replication of the SASR-CoV virus in cell culture [16], [17]. The patient also received ARBs therapy and was discontinued despite insufficient

evidence that ACE inhibitors and ARBs may cause a more severe clinical picture [18], [19], [20].

So far, it has been reported that there have been a number of disturbances in the biochemical analyses of patients with COVID-19. Lymphocytopenia is the most common finding. Necrosis or apoptosis of the lymphocytes is a possible mechanism. In non-critical patients infected with SARS CoV-2, up to 37% had mild lymphocytopenia and up to 80% in critically ill patients. In our case, there was no change in the total number of leukocytes, but there was initially a decrease in the number of lymphocytes to 0.07, with a gradual increase to 0.20. An increase in CRP to 87 was registered, followed by its normalization [21], [22].

It is known that SARS-CoV-2 binds to ACE 2 receptors and can enter the cells of the renal tubules and cause acute renal failure [15], [23], [24]. In our patient, graft function remained steady, with serum creatinine values ranged from 104 to 97 μmoll/L. Mild hypokalemia was noted in the absence of diarrhea and forced diuresis with potassium-sparing diuretics, which may be explained by the above.

SARS-CoV-2 can penetrate and replicate in hepatocytes. In 15% of patients who do not have a need for intensive care treatment, an increase in AST and ALT is observed. The same goes for the hepatic lesion in our case, with a gradual spontaneous recovery [25].

The presence of coagulopathy in COVID-19 is usually explained by a secondary bacterial infection and an increase in CRP. It is manifested by a decrease in platelet count and an increase in d-dimers, in our case 111 and 2500, respectively, and in some severe cases with the development of disseminated intravascular coagulopathy [26].

Pneumonia was confirmed by the finding of chest X-ray, as in other cases with COVID-19. Since there was no worsening in the condition, there has not been an indication for computer tomography (CT) of the lungs which is otherwise a method with a very high sensitivity of 98% for diagnosing COVID-19. Despite the extensive findings and the prolonged dry cough, the patient was without oxygen support at all times [27], [28], [29].

The use of a certain group of antibiotics such as the azithromycin has been shown to be effective in treatment. Certain centers have reported the benefits of combining it with chloroquine, but there have been those who have not responded. For severe cases, there are attempts to treat them with antiviral therapy like remdesivir. Special success has been achieved in certain cases with plasma delivery from a convalescent patient rich in antibodies. For cases combined with severe anemia in addition to blood substitution, successful *extracorporeal membrane oxygenation* (ECMO) treatments have been reported. Furthermore, tocilizumab is reported as an effective treatment in severe patients of COVID-19. However, there is still no specific therapy or vaccine for COVID-19 [30], [31], [32], [33], [34].

Conclusion

Our first experience showed that the clinical presentation of COVID-19 in a kidney transplanted recipient is the same as in the general population. Treatment with azithromycin and cephalosporin antibiotics has been shown to be effective in the treatment of bilateral pneumonia, along with the modification of immunosuppressive therapy. Since there is still no specific therapy, the latter seems to be of great importance not only for improving immunity but also for a positive clinical outcome. Experience and analysis of several cases are required to reach a conclusion about the treatment and outcome in kidney transplant recipient and COVID 19, which is the limitation in this presentation.

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