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Renal Transplants COVID-19 Infection with Different Presentations, Clinical Courses and Outcomes

Ahmed H. Elthakaby[1]and Azza Ali I. Elmenyawi[2]

Nephrology[1]and Clinical Pathology[2]Departments National Institute of Urology and Nephrology,Cairo,Egypt

ABSTRACT

We report five cases with different clinical presentations of COVID-19 infection in renal transplant patients. Initially a typical clinical presentation, in the form of CNS manifestations (amnesia, behavior change followed by left sided paresis) for the 1st case, GIT manifestations for the 2nd case and chest and cardiac manifestations for the 3rd case were presented. The other two cases similarly presented with chest manifestations but with different clinical courses. Our patients had a favorable outcome, which may provide a reference value for treating COVID-19 patients.

Keyword: Clinical manifestation, COVID19 virus infection, Renal transplant recipient.

INTRODUCTION

Respiratory droplets are considered the main mode of transmission of COVID-19 between people. COVID-19 entry to lung through binding of its S proteins to the angiotensin-converting enzyme 2 (ACE2) receptor, followed by the development of symptoms, that are ranging from coughing, fever to pneumonia[1]. Although respiratory manifestation is the most prominent symptoms of COVID-19, neurological manifestations of the virus is also reported in literature. Neurological manifestations have an incidence in 36% of the patients[2]. Non-specific mild neurological symptoms including headache, dizziness, myalgia and/or fatigue, anorexia, anosmia, and ageusia[3], are noticed in hospitalized COVID-19 patients. More-severe presentations of COVID-19 include acute stroke of varying arterial and venous mechanisms[4], confusion or/ and impaired consciousness[5], Guillain-Barre syndrome[6], meningoencephalitis[7], hemorrhagic posterior reversible encephalopathy syndrome[8], and acute necrotizing encephalopathy, affecting the brain stem and basal ganglia[9]. The proinflammatory and prothrombotic cascade as a result of cytokine storm[10], reflect other neurological manifestations because of the affection of brain vasculature and the blood brain barrier, from toxic-metabolic sequel of multi-organ dysfunction that was seen in critical illness of COVID-19. COVID19 gastrointestinal symptoms, is atypical and not a common presentation of this viral infection.

COVID 19 in kidney transplant recipients (KTRs) have varying clinical manifestations and severity, ranging from mild or asymptomatic infections to multiorgan failure resulting in death[11]. Clinical presentation of renal transplant like those of non-transplanted patients with the most frequently reported symptoms are fever (85%), dry cough (70%), myalgia (60%), and dyspnea (57%)[12].The onset of symptoms has a wide range, from 1 day to 3 weeks before the diagnosis. The severity of the infection can be aggravated with reinfection and immunological impairment leading to the development of confections with bacteria, fungus, and opportunistic pathogens. Those patients can shed virus for longer period and have increased viral load[13], in comparison to general populations.

Statement of Ethics:

Consent from the presented cases were taken and ethics approval from National Institute of Urology and Nephrology was taken.We presented a retrospective observational case series study related to new COVID-19 infection in kidney transplant population.

CASE 1

Male patient 32 years old known to have end stage renal disease (ESRD) by the age of 5 years due to reflux nephropathy. He had neurogenic bladder with bladder augmentation since 1993. He had 1st live related renal transplant from his mother that was failed 2 years after from chronic antibody mediated rejection, 2nd renal transplant from unrelated donor was done in 1996. He was on triple immunosuppressive therapy cyclosporine, mycophenolate mofetil (MMF) and prednisolone. He has stable course post 2nd renal transplant till 2018 as he had an attack of cytomegalovirus (CMV) infection that was treated by valganciclovir therapeutic dose for three weeks then prophylactic dose for three months. Renal function was normal in the 1st 15 years, Creatinine was around 1mg/dl then gradual deterioration throughout the next 10 years due to chronic allograft nephropathy, was biopsy proven with achievement of new base line of serum creatinine ranging from 1.7 to 2mg/dl. Recently he complained of deterioration of renal function, creatinine was 3mg/dl, and an attack of amnesia for short time. He was well evaluated , initial investigation revealed CBC, Hb 11.5gm/dl, WBC 2.8x10^3/ul and platelets 211 x10^3/ul. Creatinine was improved with adequate hydration to 2mg/dl.

Although Doppler US of the transplanted kidney revealed marked hydro ureter and hydronephrosis with an increase of parenchymal echogenicity with an elevated RI 0.75, decoy cell in urine was negative so

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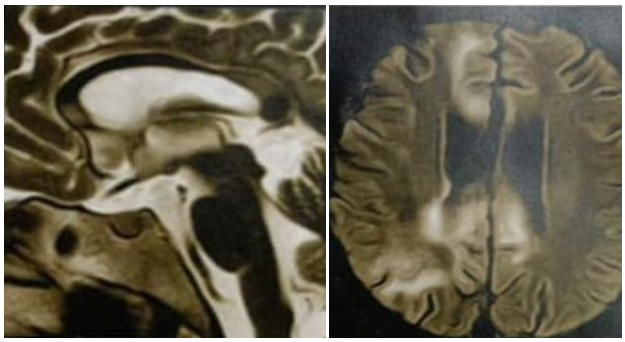
that BKV PCR was requested to rule out possible BKV related lower ureteric stricture. Condition as regard amnesia was progressed and associated with left sided hemiparesis for that MRI brain (Figure1), was done that revealed bilateral cerebral subcortical and periventricular white matter asymmetric diffuse areas of abnormal MR signals were seen displaying iso to low T1 and high / FLAIR signal with no evidence of diffusion restriction. Such signals abnormalities are seen involving both front parietal and left frontal regions and to a lesser extent the right temporal region with involvement of the subcortical U shaped fibers was noted, few foci involving genum isthmus and splenium of the corpus callosum, a condition most probably inflammatory / demyelinating or toxic process. Initially CMV, John Cunningham virus **(**JCV) and COVID 19 were requested, (results collected later on were negative for all), simultaneously the dose of MMF was decreased by 50% and started valgancyclovir 450mg/12 hours empirically to be discontinued later on. On admission, CT chest was requested that revealed bilateral pulmonary predominantly peripheral sub-pleural with basal preference small ill-defined patchy areas of faint ground glass densities/ alveolar opacities suggesting inflammatory/infectious process typical for COVID-19 CO-RAD IV for that 2nd COVID-19 PCR was sent and the result was positive. Inflammatory cytokine (IL6) was within normal range and lumbar puncture was done that revealed no conclusive results.

The patient started COVID-19 protocol including ivermectin 36mg D1, D4, D7 together with discontinuation of MMF and increase prednisolone to 30mg after a loading of 80mg for 3 days, cyclosporine was continued maintaining its level around 50 ng/ml, 3rd COVID-19 PCR was sent but was still positive.

Figure 1: MRI brain reveals bilateral cerebral white matter asymmetric abnormal areas described above with mild global brain atrophic changes. The diagnostic possibilities include inflammatory/ demyelinating and toxic process



The patient clinically was in a fluctuating course, 15 days after admission, there was no significant improvement as regard amnesia with initial mild improvement of movement of the left side upper limb > lower limb. Follow up CT chest (Figure 2), revealed multiple areas of ground glass attenuation in both lung field conglomerates to consolidative areas CORAD6. Follow up MRI brain, revealed remarkable progressive course of the previously seen right frontoparietal, perisylvian fissure and insular region white matter, abnormal signal intensity of the heterogeneous bright T2/ FLAIR signal and lower T1 signal. It was exerting the same minimal mass effect in the form of effacement of the cortical sulci. Ill-defined area of encephalomalacia was seen in the right frontal region eliciting low signal in T1 and FLAIR high signal in T2 with no diffusion restriction. A condition was of overall progressive course.So trial of IVIG 5-10 gm/day over 5 days was given but discontinued after the 3rd. dose for rising of serum creatinine > 25% of base line. Another lumbar puncture was done for COVID-19 PCR was sent and the results was negative. Plasma exchange was done for 5 sessions with significant improvement after. Also he received combined antibiotic therapy colistamycin and meropenem for the treatment of multidrug resistant Klebsiella species based on culture and sensitivity of urine for 10 days. We thought this patient probably will take few weeks to months to have acomplete recovery.

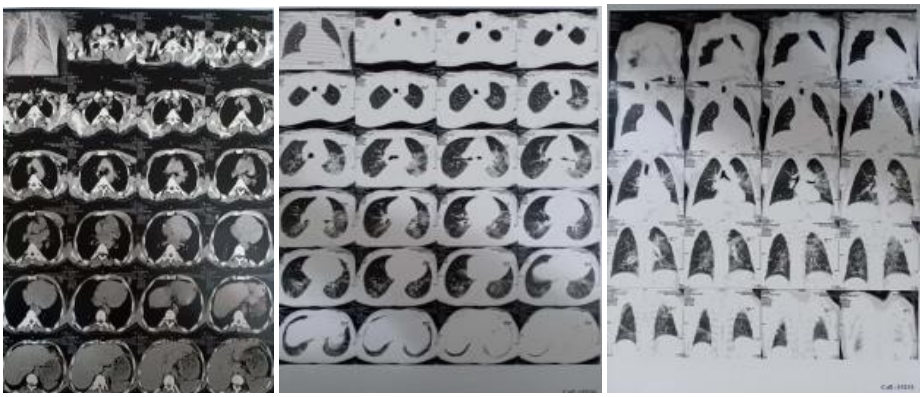


Figure 2: Follow up CT chest revealed multiple areas of ground glass attenuation in both lung fields' conglomerates to consolidative areas CORAD 6.

CASE 2

Male patient 43 years old, he underwent live related renal transplant 2years ago. He was on triple immunosuppressive therapy prednisolone, MPA, and tacrolimus (trough level 5-6 ng/ml) with stable renal function, and serum creatinine 1.3 mg /dl. Recently he was presented with fever (>38^{o}C), headache, generalized muscle pain, frequent diarrhea and vomiting that persisted for 5 days and did not respond to medical treatment.

Laboratory investigation results are shown in table 1, CMV IgG was positive and IgM was negative stool C and S and for CL difficile and Widal test were negative. High resolution CT chest revealed ground glass appearance of CORAD IV with high suspicious of COVID-19 infection that was confirmed with positive COVID-19 PCR. The patient started COVID-19 treatment protocol including ivermectin 24 mg D1, D4, D7, levofloxacin 500mg /day for 10 days, atorvastatin 20mg/ day , famotidine 40mg/day, vitamin C 1 gm/day, lactoferrin effervescent twice daily, zinc 50 mg/ day and rivaroxban 10mg/day. Together with decrease dose MPA by 50% (360mg/12hours), and increase prednisolone to 20mg ,while tacrolimus was continued at the same dose maintaining its level around 5ng/ml.

There was significant improvement of the clinical condition of the patient with disappearance of the symptoms completely two weeks after initial manifestations. The patient was advised to reassume the proper dose of MPA he was on before and to continue rivaroxban10mg/day for 1.5 months from the initial presentation.

Table 1: Laboratory results of kidney transplant cases with COVID-19 infections on 1stpresentation

Parameters	Case1	Case2	Case3	Case4	Case5
WBCs	2.8 x10^3/ul	4 x10^3/ul	8.7 x10^3/ul	4.3 x10^3/ul	4 x10^3/ul
Lymphocytes	560/ul	800/ul	1200/ul	300/ul	1400/ul
Platelets	219 x10^3/ul	167 x10^3/ul	228 x10^3/ul	159 x10^3/ul	14l x10^3/ul
Hb	11gm/dl	11.5gm/dl	14.6gm/dl	16.4gm/dl	14g/dl
CRP titre	48mg/l	29mg/l	92.3mg/l	48 mg/l	10 mg/l
LDH	------	------	1030 u/l	689 u/l	174 u/l
CPK/CKmb	------	29 /5.5 u/l	43 /6 u/l	------	------
Ferritin	124ng/ml	1493ng/ml	261ng/ml	987ng/ml	414.2ng/ml
D dimer	0.6ug/ml	0.3ug/ml	0.51ug/ml	0.15ug/ml	0.5ug/ml
SerumCreatinine	3.1mg/dl	1.33mg/dl	0.8mg/dl	2.1mg/dl	1.84 mg/dl

CASE 3

Female patient 34 years old was known to have lupus nephritis that progressed to ESRD and was maintained on regular hemodialysis for 1 year since 2009. She underwent live emotionally related renal transplantation since January 2011. She had stable renal function till now serum creatinine 0.8mg/dl. She was on triple immunosuppression tacrolimus, MMF and prednisolone. On February 2021 she had an attack of fever 39^{o}C that was resolved after 1 day and was associated with headache, generalized bony aches, and productive cough that was not responding to antibiotics treatment. Condition progressed to chest pain and palpitation at the beginning of the 2nd week from the initial manifestation, she was evaluated and her laboratory results are shown in table 1. ECG, revealed sinus tachycardia, CT chest showed evidence of ground glass appearance CORAD 5 and COVID-19 virus PCR was positive.

The patient started COVID-19 treatment protocol including ivermectin 24 mg D1, D4,D7, ceftriaxone 1gm /day for 5 days together with levofloxacin 500mg /day for 10 days, atorvastatin 20mg/ day , famotidine 40mg/day, vitamin C 1gm/day , lactoferrin effervescent twice daily , zinc 50mg/ day and rivaroxban10mg/day, together with decreasing dose of MMF by 50% (250 mg /12hours), and increasing prednisolone to 20 mg, tacrolimus was continued on the same dose to maintain its level around 5 ng/ml and verapamil was started 240mg SR 1/2 tablet daily .

There was significant improvement of the clinical condition of the patient with disappearance of the symptoms completely. The patient was advised to reassume the proper dose of MMF she was on before and to continue rivaroxban10mg/day for 1.5 months from the initial presentation.

CASE 4

Male patient 26 years old has live related renal transplant 4 years ago, with base line serum creatinine 1.3 mg/dl. He was on triple immunosuppressive therapy prednisolone, sirolimus and mycophenolic acid (MPA). He was presented 1 month before with high grade fever, cough, headache, severe bony aches and myalgia. CT chest revealed ground glass opacity CORADS V,COVID-19 PCR positive, investigation revealed the results in table 1. The patient started COVID-19 treatment protocol including ivermectin 24 mg D1, D4,D7, ceftriaxone 1gm /day for 5 days together with levofloxacin 500mg /day for 10 days, atorvastatin 20mg/ day, famotidine 40 mg/day, vitamin C 1 gm/day , lactoferrin effervescent twice daily , zinc 50mg/ day and rivaroxban10mg/day, together with decreasing the dose of MPA by 50% (360 mg/12hours), and increase of prednisolone to 20mg. Sirolimus was continued at same dose to maintain its level at 5-7 ng/ml. He had difficultyof breathing 3 days after initiation of treatment, oxygen saturation dropped to 90% necessitating besides treatment with the above protocol and hospital admission for oxygen therapy together with discontinuation of MPA.

He was discharged 5 days after with significant improvement of the clinical condition and improvement of kidney function serum creatinine 1.4mg/dl.

CASE 5

Male patient 38 years old had live related renal transplant two years ago, with base line serum Creatinine 1.2mg/dl. He was on triple immunosuppressive drugs tacrolimus, MPA and prednisolone, 2 months before he developed an attack of fever, cough, myalgia and chest pain followed by loss of taste and smell. Laboratory investigation revealed the results in table l and prograf trough level was 15 ng/ml. CT chest revealed peripherally located sub pleural ground glass densities of all lobes likely viral pneumonitis with CORADS V , COVID-19 PCR positive. The patient started COVID-19 treatment protocol including ivermectin 24 mg D1, D4,D7, levofloxacin 500mg / day for 10 days, atorvastatin 20 mg/ day , famotidine 40mg/day, vitamin C 1 gm/ day, lactoferrin effervescent twice daily , zinc 50mg/ day and rivaroxban 10mg/day, together with decrease of dose of MPA by 50% (360 mg/12hours), and increase of prednisolone to 20mg, tacrolimus was adjusted to maintain its level around 5 ng/ml. 10 days after the initial symptoms, the patient significantly improved.

DISCUSSION

There are an increased risk of serious complications from COVID-19 infection for kidney transplant recipients (KTRs) because of the use of immunosuppressive (IS) medication, elderly age (>65years), and preexisting comorbidities including diabetes, hypertension, and cardiovascular diseases[14].

COVID-19 is a respiratory virus presented mainly with pulmonary manifestations. The CNS neurological manifestations are involved in COVID-19, directly or might complicate hypoxia and thrombosis.[15, 16].

In this study, we report five renal transplanted cases with COVID-19 infection who presented with different clinical manifestations. The primary suspicion was based on symptoms, chest CT scan, that may be useful tools for rapid diagnosis of COVID-19 infection with a low rate of missed diagnosis (3.9%, 2/51) but its limitation exist for inability of identifying and differentiating between specific viruses[17]. So it was confirmed by real-time RT-PCR assays through a nasopharyngeal

swab of the upper respiratory secretions with high specificity > 99% and variable sensitivity based on the severity of disease, specimen, and assay types[18]. Its false negatives results are up to 30%, positivity may be improved with repeated tests on successive occasions that was done in case **(1)**[19].

Case 1 presented initially with amnesia for short time, followed by behavior changes and lastly left sided paresis. There was no studies published about cognitive complications of COVID-19 infection including memory impairment or attention. CNS manifestations in COVID-19 infections were rare but reported as an initial clinical presentation. Neurological manifestations varying from dizziness and headache, to cerebrovascular disease are noticed in 36.4% of 214 hospitalized COVID-19 patients[2]. While Helms *et al*.,(2020)[(7)],reported that 84 percent of 58 COVID-19 intensive care (IC) patients had neurological symptoms, with more deterioration of the cognitive function of the brain that was complicated with neurological insult. MRI brain was done to our patient, as neuroimaging features that may contribute to the diagnosis[20]. It revealed a condition most probably inflammatory / demyelinating or toxic process. For that polyoma virus screen was done (JCV PCR and BKV PCR) specially there was association of moderate hydroureter and pelvicalyceal dilatation of transplanted kidney.

Beek *etal*., (2007)[(21),] revealed that JCV infection leads to progressive multifocal leukoencephalopathy that leads to demyelination, its symptoms includes focal neurological deficit, sudden loss of consciousness and visual changes. The brain MRI shows asymmetric, non-enhancing, T2 hyper intense lesions – usually in the subcortical regions. On the other hand neurological manifestations of the herpes virus family include[17], limbic encephalitis-like syndrome (HSV CMV, HHV-6), rhomb encephalitis, ventriculitis, myelitis, vascular involvement (VZV), and a multisystem post-transplant lymphoproliferative disorder (PTLD), which may involve the CNS and is associated with the Epstein-Barr virus (EBV) [22]. As a result of HSV, EBV (IgG, IgM), CMV, BKV and JCV PCR were negative so screening protocols of COVID-19 should be considered in the presence of an atypical CNS presentation since the increase in the number of cases and evidence of asymptomatic transmission among the community and contact with infected individuals. So high resolution CT chest was done suggesting inflammatory /infectious process that was typical for COVID-19 CO-RAD IV[17].

Real time (RT) PCR of COVID-19 was done and initially was negative. Although RT-PCR is confirmative for diagnosing COVID-19, it may have suboptimal sensitivity, due to an early stages of COVID-19, the viral load is below detection limit or sampling errors[23], 2nd RT PCR for COVID-19 was done that was positive before which lumbar puncture for the patient was done for cell count, pan culture, viral study and chemistry with the results were normal. In the other cases CT chest was diagnostic and was confirmed with RT PCR for COVID-19 that was positive. Thereare a similarity in KTR and non-transplant population regarding laboratory results[24]. Our cases results revealed (table1), the white cell counts were (median 4000/mm^3), a relative lymphopenia (median 800 lymphocytes /mm^3) and platelet counts were within normal limits[25]. Serum ferritin (median 414.2 ng/mL) was elevated in our study. D dimer (median 0.5 ng/ml) was borderline; some patients were elevated while the others were normal. Our treatment protocol regarding maintenance immunosuppression, the primary aim was to balance between the risk of rejection and over immunosuppression complications, including COVID-19 worsening complications and super infections. Three of our presented cases were treated at home whose symptoms either GIT manifestation and pulmonary manifestation were not complicated, so we decrease the antimetabolite dose by 50% as their clinical manifestations were mild to moderate in severity with no need for them to be admitted in the hospital.

The other two cases one presented with CNS manifestation that was severe in nature and complicated with pulmonary manifestation, the other had pulmonary manifestations that complicated with shortness of breath and hypoxia, oxygen saturation 90% and for both patients antimetabolites discontinued completely. Initially for all cases, prednisolone dose was increased to 20mg /day and tacrolimus and sirolimus level were maintained around 5ng/ml. Cyclosporine was maintained at a level of 50 ng/ml. Managing immunosuppression in transplant patient with COVID-19, in mild infections, usually there is continuation or reduction of the dose of antiproliferative drugs (mycophenolate mofetil), which its discontinuation is preferable while monitoring the patients closely. In severe cases requiring mechanical ventilation, we can even discontinue calcineurin inhibitors with continuation of corticosteroid therapy. Undoubtedly, the treatment should be individualized based on the careful assessment of each patient[26]. Although most cases had immunosuppression reduction, others studies reported patients who maintained immunosuppression were recovered successfully[27].

All our cases received anticoagulation as prophylactic dose based on the level of D- dimer, based on the fact that coagulopathy and disseminated intravascular coagulation are common and associated with severe illness and death in COVID-19[28]. Critically ill patients can present with

microvascular thrombosis, venous and pulmonary thromboembolism, and acute arterial thrombosis[29].
All cases received low dose prednisolone 20mg/day with the unique case 1 from progressive course of CNS manifestationas he received initially 80mg/day for 3 days then maintained on 30mg/day. Two weeks after due to the progressive nature of CNS lesion he received pulse methylprednisolone 500mg x1x5. Although corticosteroid use in COVID-19 is not strongly advised by many retrospective studies, the RECOVERY trial found the use of dexamethasone is accompanied with a significant reduction in death in severe case on ventilator or moderate case on supplemental oxygen therapy but of no benefit in mild to moderate case requiring no oxygen. Non specific treatment was received by all cases, in the form of ivermectin 500ug/kg D1, D4, D7, vitamins and zinc supplement, lactoferrin and levofloxacin 500mg/ day for 10 days. Chaccoura and his colleagues (2020) [(30)], revealed that the use of a single 400 mcg/kg dose of ivermectin within 72 hours of fever or cough onset in non-severe COVID-19 patients, there was marked improvement of anosmia/hyposmia, cough, reduction in viral loads and lower IgG titers but there was no difference in the proportion of PCR positive tests.Specific treatment for case 1 for his progressive nature of CNS manifestation was used. He was given low dose IVIG 5-10 gm daily that was discontinued after the 3rd dose as a result of deterioration of renal function. He was shifted to plasma exchange, initially there was a gradual improvement of the clinical condition of the patient. Zhou et al., (2020)[(31)], reported that,COVID-19 critical cases can be treated with combined low-dose corticosteroid and immunoglobulin that can reduce the effect of COVID-19 related inflammatory storm, improve the passive immunity and reduce the risk of secondary infections. This patient received 5 session of plasma exchange with significant improvement of his manifestation. Therapeutic plasma exchange (TPE), that was performed in severe COVID-19 patients has been associated with improved outcomes, it should be utilized earlier in critically ill patients within 7 to 14 days of onset of illness however, and randomized controlled clinical trials are warranted to draw final conclusive findings[32].
Indeed**,** Cao, *etal*., (2020)[(33),]reported that, combining TPE and corticosteroids can be effective in the treatment of severe COVID-19 related encephalitis. Finally,the patient received combined antibiotic therapy colistamycin and meropenem for the treatment of multidrug resistant Klebsiella species based on culture and sensitivity of urine. Outcome of our cases are favorable. They all survived with complete recovery in four cases 2 weeks after the appearance of symptoms and one case almost recovered but resuming his normal activity will take time. In general, outcomes of kidney transplant patients are worse than those of the general population. Early reports suggest similarity of COVID-19 mortality between dialysis-dependent ESKD and kidney transplant patients, with amorality range between 16% and 30%**, as** reported by the New York studies[12,24].

CONCLUSION

Most of transplant recipients with COVID-19 presented with similar symptoms, laboratory values, imaging, and outcomes to those of immunocompetent patients. Although the five presented renal transplant recipients had a favorable outcome, they had different clinical presentations and may had different clinical courses, which may provide a reference value for treating such patients.

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