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Title

Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19)

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Abstract

During the novel coronavirus pandemic, organ transplant recipients represent a frail susceptible category due to long-term immunosuppressive therapy. For this reason, clinical manifestations may differ from general population and different treatment approaches may be needed. We present the case of a 36-year-old kidney transplanted woman affected by Senior-Loken syndrome diagnosed with COVID-19 pneumonia after a contact with her positive mother. Initial symptoms were fatigue, dry cough and coryza; she never had fever nor oxygen supplementation. Hydroxychloroquine and lopinavir/ritonavir were started, and the antiviral drug was replaced with darunavir/cobicistat after two days for diarrhea. Immunosuppressant levels were closely monitored, and we observed very high tacrolimus trough levels despite initial dose reduction. The patient was left with steroid therapy alone. The peculiarity of clinical presentation and the management difficulties represent the flagship of our case-report. We stress the need for guidelines in transplant recipients with COVID-19 infection with particular regard to the management of therapy.

Introduction

At the end of December 2019, a novel Coronavirus, (SARS-CoV-2, previously known as 2019-nCoV) was identified as the causal pathogen of an ongoing pandemic. The first cases were reported in Wuhan, China, and then they spread to other countries worldwide, posing great threats to public health. Very recently an outbreak in Italy is occurring with a subsequent concern regarding the Italian national health system's capacity to effectively respond to the needs of

patients who are infected[1]. Among them, organ transplant patients represent a frail susceptible category due to long-term immunosuppressive therapy. For this reason, clinical complications of COVID-19 infection may differ from those of the general population and need different treatment approaches[2]. Herein, we present the case of a 36 year-old woman with Senior-Loken syndrome who underwent a 2nd kidney transplant in 1995 and developed a pauci-symptomatic COVID-19 pneumonia in the early stage of the outbreak in Tuscany, Italy.

Case report

The patient is a 36 year-old woman with Senior-Loken syndrome (SLS). SLS is a rare genetic disorder characterized by nephronophthisis and retinal degeneration leading to blindness and end stage kidney disease (ESKD). Following ESKD, she underwent living-donor kidney transplantation in 1993 from her mother, a common consequence of her genetic disorder. The transplant was complicated by Delayed Graft Function (DGF) and failed in 1995, so in the same year she received a second transplant from cadaveric donor. The induction therapy comprised basiliximab, cyclosporin, mycophenolate mofetil and corticosteroids. Since 2013, the immunosuppressive therapy was switched to tacrolimus and corticosteroids. Her serum creatinine levels stabilized between 1.5-1.8 mg/dl and her tacrolimus trough levels ranged between 5-7 ng/mL.

At her most recent follow-up on 20th January 2020 her serum creatinine was 1.5 mg/dL and her tacrolimus trough level was 8.8 ng/mL.

She lived with her mother between Florence (Tuscany, Italy) and Rebecco d'Oglio (Cremona, Lombardy, Italy). Her mother had visited some relatives in Rebecco d'Oglio (hot spot of the COVID19 outbreak) at the end of February. On 5th March, due to loss of consciousness, her mother was hospitalized in the Infectious and Tropical Diseases unit of our hospital (Careggi Hospital,Florence) and a diagnosis of COVID-19 pneumonia was made.

On 6th March 2020 a rhino-pharyngeal swab sample for reverse real-time polymerase chain reaction (PCR) for SARS-CoV-2 was obtained from the patient, since she had been in contact with her mother and showed mild symptoms compatible with COVID-19 infection (dry cough) beginning 1st of March; the swab was positive and so the patient was hospitalized.

The patient initial symptoms were: fatigue, dry cough, coryza. She never had fever. Physical examination on admission revealed a body temperature of 36.3°C, blood pressure of 120/80 mmHg, a pulse of 85 bpm, respiratory rate of 17 breaths per minute, and oxygen saturation of 99% in room air.

Her laboratory results and radiological features were as follows: lymphocyte count were normal according to age; neutrophil count was markedly high (17.20x10^9/L); creatinine level was 2.29 mg/dL, eGFR 27 ml/min; C-reactive protein (CRP) was significantly elevated (67 mg/L); serum levels of some inflammatory cytokines were tested in two different occasions: interleukin (IL-1beta), IL-10, IL-6 were in normal range while IL-8 was slightly elevated (Table 1); chest X-ray showed reticulonodular left lung opacity with perivascular infiltrates especially in the perihilar region.

These abnormalities confirmed the diagnosis of COVID-19 pneumonia. The background therapy was tacrolimus 5 mg bid, methylprednisolone 4 mg daily, omeprazole 20 mg daily, allopurinol 150 mg daily, atorvastatin 20 mg daily and ramipril 2.5 mg daily. On admission, antiviral therapy with lopinavir/ritonavir (400mg/100mg bid), along with

hydroxychloroquine (200mg bid) and ceftriaxone 2g daily was started. Atorvastatin was stopped. Adjustments based on drug-drug interactions (DDI) with her routine therapy were considered, the immunosuppressive therapy was initially reduced with tacrolimus 3 mg bid and methylprednisolone 6.5 mg daily. Therapy with lopinavir/ritonavir was then replaced on day 2 with darunavir/cobicistat 800mg/150 mg due to the onset of nausea and diarrhea. Tacrolimus trough level on this day was not available due to analytical issues.

On day 4 she started to complain intermittent abdominal pain, nausea and vomit. Blood gases were normal with pH 7.43, pO2 88.2mmHg, pCO2 26.6mmHg, $HCO3^-$ 20 mmol/L, K+ 4.6 mEq/L, Na 138 mEq/L, Ca 4.89mg/dL, Cl 112 mEq/L. Tacrolimus trough levels turned to be extremely high (90.5 ng/mL); ECG was normal. We immediately discontinued both antiviral therapy and tacrolimus, starting daily monitoring of tacrolimus trough levels (Table 1). In the following days the patient recovered from her gastrointestinal symptoms and showed a general amelioration of clinical condition, notably a decrease of fatigue and cough, with stable SpO2 levels (98% room air). Tacrolimus trough levels progressively decreased during the following days, reaching the value of 18.8 ng/mL the day of discharge (Table 1). The patient was discharged together with her mother on day 9 and put in home isolation until two consecutively negative rhino-pharyngeal swabs, scheduled on day 12th and 18th after discharge. Tacrolimus trough levels were monitored with twice weekly home blood sampling, showing a value of 19 ug/mL a week after discharge and of 15 ug/mL after two weeks. The last creatinine level was 1,75 mg/dL, eGFR 37 ml/min. The patient, since hospital discharge, is on corticosteroid therapy alone.

Discussion

The infection caused by SARS-CoV-2 was declared global pandemic by WHO. In the past, other coronaviruses caused epidemic outbreaks: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were also reported in solid organ transplant recipients[3,4]. Data on the clinical presentation of COVID-19 in solid organ transplant recipients are lacking.

We hereby discuss the first Italian reported COVID-19 infection in a kidney transplant recipient. To date, only two other case reports are available, one Chinese and one Spanish.

Lan Zhu et al. described a successful recovery of a kidney transplant patient following a treatment regimen consisting of reduced immunosuppressant use and low dose methylprednisolone-based therapy. The patient's illness was severe, and they argued that both the anti-inflammatory and graft-protective effect of steroids (along with novel therapies) seemed to be crucial for the patient's clinical improvement. At first, immunosuppression was reduced by lowering the dosage of the calcineurin inhibitor and mildly increasing methylprednisolone like in other cases of opportunistic infections in kidney transplant recipients. This approach, the mainstay for severe viral infections, appears to be safe in patients with mild SARS-CoV-2 infections, although more evidence-based data are needed[5].

Another approach used is the prompt suspension of calcineurin inhibitors, mycophenolic acid and m-TOR inhibitors, continuing immunosuppression in monotherapy with methylprednisolone. There is currently no evidence to support immediate discontinuation of maintenance corticosteroids in kidney transplant recipients. On the other hand, it is not currently possible to have evidence that in COVID-19 patients corticosteroids monotherapy has better outcomes than corticosteroids combined with a second immunosuppressive drug.

The peculiarity of this case resides in the clinical presentation, as the patient did not develop a severe form of COVID-19 despite receiving immunosuppressive drugs. More recently, indeed, Guillen et al. described a case of COVID-19 in a recipient of a 3rd deceased-donor kidney transplant pointing out the importance of atypical symptoms in the setting of an immunosuppressive therapy[6].

Atypical presentations in immunocompromised host, consisting in delayed symptom development, prolonged incubation period and persistent viral shedding without clinical deterioration have been well described in other CoV infections and they should always be put into account in order to control potential outbreaks in such kind of patients.

In our case, the atypical manifestations misled us so that we did not stop neither reduce immunosuppressive drugs causing an overdose of tacrolimus. Pharmacokinetic profiles of tacrolimus is influenced by CYP3A4 and P-glycoprotein, and it is presumable that drug-drug interactions can change the drug blood level. Drug as lopinavir/ritonavir that competitively inhibits CYP3A4 activity, can increase the bioavailability of tacrolimus and other calcineurin inhibitors, with potential for toxicity. It is therefore necessary to weigh the risks and benefits in using these drugs in the transplant population. The most recent evidences regarding lopinavir/ritonavir treatment show that they did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19[7].

Other novel therapies (such as remdesivir, tocilizumab) could be useful but they are reserved to patients with severe pneumonia and there are no data on safety on solid transplant recipients. Treatment with the malaria drug hydroxychloroquine could be a more feasible option.

Even in the acute phase the patient did not show considerable respiratory manifestations despite the presence of radiological pneumonia findings. The symptomatology only worsened due to drug-related gastrointestinal toxicity. From day 4 (stop of immunosuppression) we observed a reduction in inflammatory parameters (CRP, IL-6). It could be possible that increased corticosteroid therapy has reduced IL-6 levels, recently involved as one of the main factors in the progression of COVID-19 pneumonia[8].

To date, Acute Kidney Injury (AKI) was found to be an independent predictor of mortality in CODIV-19 infection[9]. However, in our case the most reasonable effect on GFR was due to excessive tacrolimus exposure, owing to the well-known interaction between tacrolimus and ritonavir[10].

As high viral load and close contact are a risk factor for transmission, appropriate airborne infection isolation room and careful wearing and removal of Personal Protective Equipment (PPE) is required in managing such patients. Considering these aspects, patients who cannot avoid corticosteroid therapy should be aggressively managed from symptom onset, including evidence based, if present, or experimental therapeutic measures such as antiviral therapy.

In conclusion, we want to point out the importance of a quick diagnosis of COVID-19 especially in the presence of atypical symptoms. In the next months, we suggest COVID-19 to be rule out by performing rhino-pharyngeal swab sample to all the kidney transplanted recipients presenting with a suspicious history. We also intend to underline the need for guidelines in renal transplant recipient with COVID-19 infection with particular regard to management of therapy.

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Author's contribution

M.B, B.B, An.B and M.T. treated the patient. An.B, G.L., Al.B. and M.T collected and analyzed the clinical data and wrote the manuscript. M.B and B.B supervised data analysis and preparation of manuscript. An.B and G.L reviewed and edited the final version of manuscript. A.V., Al.B. and C.C. provided academic leadership;
All authors approved the final version of the manuscript.

Table.1 Blood exams during hospitalization.

	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 9	Normal range
Tacrolimus (ng/mL)	-	90.5	81.5	74.5	72.4	33.8	18.8	5-15
Creatinine (mg/dL)	1.77	1.77	2.19	2.21	1.98	1.91	1.75	0.6-1.2
CRP (mg/L)	67	-	131	70	-	5	-	<5
IL-6 (pg/ml)	-	-	10.3	-	2.5	-	-	0-10
IL-8 (pg/ml)	-	-	-	-	31	-	-	-
IL-10 (pg/ml)	-	-	2.5	-	2.1	-	-	0-15
IL-1 beta (pg/ml)	-	-	1	-	1	-	-	-