



Case Report

Are CMV and SARS-CoV-2 Infections Mutual Risk Factors in Kidney Transplant Recipients?

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Abstract: Throughout the years, much progress has been made in the field of renal transplantation; however, along with new developments, new problems have arisen. While transplantation is the optimal choice in patients suffering from end-stage renal disease, it is always connected to certain commonly associated risks, in particular those caused by opportunistic infections. One such risk includes the reactivation of cytomegalovirus (CMV), an issue commonly affecting all kinds of transplant recipients. Similarly, with the rise of the ever-evolving global SARS-CoV-2 pandemic, patients must be constantly monitored for any respiratory symptoms, and observed closely under the care of their attending physician. Treating these patients has become extremely difficult due to limitations caused by COVID-19 protocols (for instance, the reduction of immunosuppression dosages and the avoidance of lymphocyte-depleting induction therapy) and the lack of knowledge surrounding this relatively new and worsening risk factor. In order to give patients optimal care, these arising problems need to be studied and addressed.

Keywords: COVID-19; kidney transplantation; cytomegalovirus



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1. Introduction

There are many challenges to take into account regarding the treatment plan for renal transplant recipients, including the risk of infections, such as cytomegalovirus infection (CMV). Nowadays, due to the COVID-19 pandemic, these concerns only continue to grow, and new problems present themselves, including the possibility of one infection predisposing to another. Transplant recipients often present multiple diagnoses, and by focusing entirely on only one (be it COVID or any other), the other diagnoses may go completely unnoticed. Moreover, transplant recipients may present comorbidities, such as diabetes or cardiovascular diseases, which are also risk factors connected with severe COVID-19 (coronavirus disease 2019) cases [1]. Additionally, a severe course of COVID-19 is associated with lymphopenia, a state that can also be connected with CMV infections in renal transplant recipients [1,2].

Further studies need to be conducted to better understand the relationship between these two infections (CMV and COVID-19) in kidney transplant recipients, as well as to explore their impact as a dual infection, to properly combat these pathogens. This includes investigating any other possible complications that may emerge, and determining whether these two viral infections are predisposed to each other, or towards other infections, and in such a case, the underlying mechanism.

We report a case of CMV in a renal transplant recipient that later becomes infected by COVID-19, and experiences both severe dyspnoea and new-onset peripheral edema, the latter resulted from the provided treatment.

2. Case Presentation

A 49-year-old female with a history of polycystic kidney disease (autosomal dominant polycystic disease, ADPKD), with a low immunity and without any induction therapy, had undergone a left-sided nephrectomy in preparation for transplantation, and the transplanted kidney was implanted into the left iliac fossa in the summer of 2020. At the time of transplantation, both the donor and transplant recipient were positive for CMV IgG antibodies. There was no prophylaxis against CMV prescribed; however, co-trimoxazole prophylaxis was administered for the first six months following transplantation. After experiencing a delayed graft function, requiring temporary hemodialysis, chronic graft function impairment was observed, concomitant with a serum creatinine level of 2.8 mg/dL and eGFR of 19 mL/min.

Three months post-transplantation, the patient came in for a routine follow-up appointment to monitor kidney function at the outpatient transplant clinic, with the following complaints: pharyngitis, gingivitis, and stomatitis, as well as gastric pain for the past five days. The patient received chronic immunosuppressive treatment that consisted of prednisone (15 mg), tacrolimus (8 mg/daily), and mycophelate mofetil (1000 mg/daily). Upon inspection, the patient had a blood pressure of 150/88 mmHg, and her complete blood count revealed lymphopenia. Her lymphocyte level had decreased from $2.21 \times 10^3/\mu\text{L}$ (20.3%) to $0.360 \times 10^3/\mu\text{L}$. The blood tests also revealed a white blood cell count of $2.99 \times 10^3/\mu\text{L}$ (which previously had been $6.83 \times 10^3/\mu\text{L}$), a hemoglobin level of 9.6 g/dL (previously 12.1 g/dL), a hematocrit level of 30.5% (previously 30.1%), and a platelet count of $127 \times 10^3/\mu\text{L}$ (previously $181 \times 10^3/\mu\text{L}$). The level of C-reactive protein was also elevated (which rose from 6 to 21 mg/L), and her procalcitonin level was also slightly elevated (0.07 above the upper limit of 0.05 ng/mL), while her liver transaminase level was within normal limits. In the midst of a global pandemic and the flu-like symptoms, to exclude the possibility of COVID-19 infection, the patient underwent testing for COVID-19 (RT-PCR), the result from which turned out to be negative. At this time, the patient denied any symptoms of anosmia or ageusia. She was additionally tested for CMV, which resulted in a positive test result, and exhibited a blood CMV replication count that reached 7.5×10^5 CMV copies/mL. Following this, mycophenolate mofetil was discontinued and ganciclovir was administered IV (2.5 mg/kg/24 h). Although the treatment resulted in a raised white blood cell count of $6 \times 10^3/\mu\text{L}$, the lymphocyte count decreased to $1.37 \times 10^3/\mu\text{L}$.

Eight weeks later, during the next follow-up visit, a standard test for both COVID-19 and CMV replication was performed; the result of which was negative for both. During this time, the patient was also diagnosed with steroid-induced diabetes, and was consequently prescribed linagliptin (5 mg once daily). Two weeks after, the patient was admitted to the emergency department of a local hospital, where she presented with fever, generalized weakness, and breathlessness even while performing simple tasks. During the physical examination, the following findings were noted: dyspnea at rest, lung crepitations (detected via auscultation), and an oxygen saturation level of 70%, all of which suggested a diagnosis of COVID-19. At this time, the patient tested positive for COVID-19, and was then transferred to a dedicated COVID-19 hospital.

During the patient's stay at the COVID-19 care center, laboratory tests were performed that revealed a decreased lymphocyte level (of approximately $500/\mu\text{L}$) and a blood gas value within normal limits. The serum creatinine concentration was elevated (just over 4 mg/dL), suggesting an episode of acute kidney injury, and as a result, a chest CT angiography was not ordered. Instead, a chest X-ray was performed, which revealed extensive bilateral lesions. Immediately, oxygen therapy was introduced, and the patient was retested for COVID-19 (RT-PCR), the result of which turned out to be positive once more. At the time, the blood oxygen saturation was 99%, the pulse rate was 92 beats/min, and the blood pressure was 130/75 mmHg. The patient required supplemental oxygen therapy, which consisted of a reservoir mask and a flow rate of 10 to 15 L/min. She was subsequently prescribed IV hydrocortisone (100 mg once daily), levofloxacin, and low-molecular-weight heparin subcutaneously, as treatment. In addition, convalescent plasma was administered.

After successful therapy, and upon testing negative for COVID-19 (RT-PCR), the patient was transferred to the Department of Nephrology and Transplantation Medicine for further treatment. She continued to experience dyspnoea, and presented with extensive new-onset peripheral edema. A chest ultrasound revealed pleural fluid, and a CT scan later confirmed the diagnosis of pleural effusion (measuring roughly 7.7 cm on the right side and 5.4 cm on the left). A high dose of loop diuretic was administered, which was ineffective; thereafter, the recipient instead underwent two weeks of ultrafiltration sessions at the dialysis center. Following this procedure, the patient had lost 20 kg of body weight. Moreover, ensuing the loss of her oedema, her respiratory symptoms vanished as well. She was once again tested for CMV, and 292 copies/mL were detected; she was then successfully treated with IV ganciclovir in prophylaxis at a dose of 1 mg/kg/24 h.

Thereafter, the patient experienced pain localized within the right kidney, and an ultrasound as well as a CT scan of this area revealed a heterogeneous hypoechogenic area (approximately 7.0 cm by 4.3 cm by 10.0 cm in size). Microbiological tests of the drained pus revealed a *Klebsiella pneumoniae* infection, and the appropriate antibiotic therapy was administered, followed by a nephrectomy of the right kidney. Consequently, there were no post-operative complications, and the patient reached a full recovery, with stable kidney allograft function at the level observed before CMV and COVID-19 infection (an eGFR of approximately 20 mL/min). Three weeks following the nephrectomy, mycophenolate mofetil was readministered.

3. Discussion

We describe a case where a kidney transplant recipient presents with a CMV infection, to later be infected with COVID-19.

One of the leading predicaments of managing post-transplant solid organ patients is treating active cytomegalovirus infections. CMV is widespread in the human population because of its easy transmission routes via saliva or blood [3]. The presence of anti-CMV antibodies varies from 45% to 100%, depending on the analyzed adult population [4]. Immunocompetent individuals often present with a primary asymptomatic infection that is later followed by a period of viral latency, while immunocompromised patients are at an increased risk of reactivation [5]. Symptomatic CMV replication develops in approximately 8% to 32% of renal transplant recipients without any antiviral prophylaxis [5]. This reactivation often leads to multiple complications, including loss of graft function [6,7], transplant rejection [6], and secondary infections [8].

SARS-CoV-2 is a virus from the family Coronaviridae that is responsible for causing the disease known as COVID-19 [9]. The course of COVID-19 varies from being asymptomatic to having severe pneumonia with numerous complications, such as acute respiratory distress syndrome (ARDS), sepsis, multiple organ dysfunction, and secondary infections [10]. While a majority of the infected population presents asymptotically, or with mild symptoms, severe COVID-19 is often associated with risks such as immunosuppression [11]. Renal transplant recipients in particular have an increased tendency for contracting COVID-19 (a percentage of approximately 0.8% to 5%), in comparison to the incidence of 0.2% in the general population [12]. Additionally, the mortality rate in renal transplant recipients, which varies from 22% to 28% [13], is much higher than in confirmed cases of COVID-19 in the general population (fatality is reaching a total of roughly 0.23% in the global population) [14].

There are few papers reporting the incidence of SARS-CoV-2 and CMV co-infections, particularly in elderly or immunocompromised patients [15–17]. The first documentation of such a case was reported for a 91-year-old woman that was admitted to Chieti Hospital with symptoms of an acute infection. Her blood tests revealed lymphocytopenia and increased levels of inflammation markers. Chest X-rays were later performed that confirmed bilateral pneumonia, and the patient was then tested for both SARS-CoV-2 and CMV, which yielded positive results for both [15]. Another paper describing how CMV infections can act as a complication of COVID-19 was published by Moniz et al., in which five immunosuppressed

patients were admitted to the hospital with dyspnoea and other respiratory tract infection symptoms. All of these patients tested positive for SARS-CoV-2, and one patient was additionally tested for CMV, the result of which turned out to be negative. Later during their hospitalization, all of these patients were tested for CMV and all were positive; this finding suggests that, in this instance, CMV resulted as a secondary infection of COVID-19 [17].

Kidney transplant recipients are a group of patients at an increased risk for CMV and SARS-CoV-2 co-infections resulting from immunosuppressive treatment. The first four cases of CMV and COVID-19 co-infections in post-renal transplant patients were reported by Molaei et al. Blood tests on these patients revealed lymphocytopenia, with lymphocyte counts between 88 to 400/ μ L [18]. In our patient's case of CMV reactivation, it occurred roughly three months prior to the SARS-CoV-2 infection, and the CMV replication was accompanied by lymphocytopenia. The next case of CMV reactivation appeared shortly after our patient was discharged from the COVID care center.

Our patient did not present with a case of co-infection, but rather a mutual connection between the two viral infections was observed. We consider that the previous instance of CMV reactivation resulted in lymphopenia, which may have predisposed our patient to a SARS-CoV-2 infection.

CMV infection affects the immune system mainly through NK-cells and cytotoxic T-cells [16,19]. During this infection, the number of naive lymphocytes decrease in connection with the elevated levels of CMV-specific cytotoxic T-cells and NK-cells in the peripheral blood [16,19]. These cells play a primary role in cell-mediated immunity, acting against viral pathogens, and this is mainly due to the interaction between CD4+ and CD8+ T-cells [20]. CMV expresses proteins that inhibit the activation of T-cells and downregulate the presentation of MHC class II molecules on infected cells. Furthermore, CMV-infected macrophages release IL-10 or TGF- β , which are negative regulators of T-cell activation and proliferation [20].

SARS-CoV-2 acts synergistically with CMV to decrease the number of T lymphocytes and NK-cells. This process results in immunosuppression, and consequently, in patients affected by either virus, allows them to be infected by other pathogens [21]. In our patient's case, we believe SARS-CoV-2 infection may have predisposed them to a reactivated case of CMV. Additionally, we regard the persistent lymphopenia, which followed the previous CMV and COVID-19 infections, to act as a predisposing factor for the abscess (a secondary bacterial infection) of the polycystic kidney. Nevertheless, the potential that such an infection could be caused by the risk of inserting a bladder catheter needs to be taken into consideration. We theorize that the lymphopenia caused by CMV can predispose our patient to COVID-19 infection, and the reverse situation may occur. The reactivation of CMV seen in our patient after being cured of COVID-19 suggests that SARS-CoV-2 may play a role as a triggering factor, increasing our patient's susceptibility to other infections. In fact, lymphopenia is one of the most common laboratory findings in patients with COVID-19, and is even linked to 96.1% cases of severe SARS-CoV-2 infections [22]. Lymphopenia experienced during COVID-19 is mainly associated with the decreased number of T-cells in the CD4+ and CD8+ population [22]. There are many suggested mechanisms that may explain this change in lymphocyte count during a SARS-CoV-2 infections, which include: the induction of lymphocytic apoptosis, which is stimulated by a cytokine storm; the redistribution of lymphocytes into infected tissues; and the suppression of main immune organ function, due to viral mechanisms [22]. Studies on convalescent donors that have recovered from COVID-19 revealed that, although the lymphocytic population remained within the norm or even increased, the number of CD4+ T-cells and B-cells were persistently decreased, even two months after a successful recovery from COVID-19 [23].

Immunosuppressive drugs used in standard treatment therapies for post-transplant recipients, in particular glucocorticosteroids, which are known to cause T-cell suppression, are frequently attributed to CMV-related complications in these types of patients [24]. Similarly, a higher incidence of CMV in these patients is related to this specific medication;

however, how glucocorticosteroids influence CMV has not yet been determined [24]. The use of such drug therapies should be considered in our patient's case as a possible explanation for the observed lymphopenia. Likewise, the hydrocortisone administered during COVID-19 treatment may have lowered our patient's lymphocyte count.

Prior to the COVID-19 hospitalization, when lymphopenia was originally discovered, one of the immunosuppressant drugs, mycophenolate mofetil, was reduced, and afterwards discontinued. This resulted in normalized lymphocyte levels, but regardless, our patient became severely infected with COVID-19, which led to the question of how CMV infections may impact COVID-19 infections, and vice versa. Studies on COVID-19 convalescent donors have revealed decreased numbers of CD4+ T-cells and B-cells [23]; similarly, post-allogeneic hematopoietic stem cell transplantation patients with CMV reactivation demonstrated a decrease in CD4+ T cells and B cells [25]. While further studies need to be conducted, perhaps the possible influence the two viral infections may have on each other is related to the similar mechanisms of decreasing CD4+ T-cells and B-cells.

4. Conclusions

In the context of this ongoing worldwide COVID-19 pandemic, often times there is a primary focus on the diagnosis of COVID-19, rather than on other associated particulars of the disease. These include protocol limitations, such as decreasing immunosuppressive dosages involved with COVID-19, as well as any rising complications, such as lymphopenia, or the lack of data available for analyzing how this particular infection interacts or may be predisposed to other infections. Additionally, it may divert attention from other possible diagnoses, or the understanding that there may be more than one possible diagnosis in these patients.

COVID-19 is a complex disease, and one that requires taking multiple factors (such as modifying immunosuppressants and the surveillance of drug-to-drug interactions) into account, especially when monitoring and treating renal transplant recipients. Kidney transplant recipients are already at an increased risk of other opportunistic infections, such as CMV, and for having other common comorbidities, for instance diabetes. The above-mentioned factors are expected to increase their likelihood of contracting COVID-19, and make it even more difficult to treat this distinct group of immunosuppressed patients. Therefore, it is essential to conduct further studies on these discussed issues, particularly regarding the connection between COVID-19 and CMV infections in renal transplant recipients.

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