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CMV Infection Following mRNA SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients

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Cytomegalovirus (CMV) is a common herpes virus that infects 60%–100% of adults and is one of the main causes of infection after organ transplantation.[1] In transplant recipients, CMV infection may occur because of transmission from the transplanted organ, reactivation of latent infection, or primary infection in a seronegative host.[2] In solid organ transplants, CMV infection is associated with poor short-term and long-term outcomes including allograft function and survival.[3-5] There are several factors that can lead to an increased risk of CMV primary infection and reactivation, including intensity of immunosuppression, use of lymphocyte-depleting therapies, acute rejection, and advanced age in the donor or recipient. Human leukocyte antigen mismatch, or immunologic incompatibility between donor and recipient based on white blood cell and tissue surface proteins; concurrent infections (such as with herpes virus 6 or 7); and genetic polymorphisms are also major risks for CMV reactivation.[2]

Coronavirus disease 2019 (COVID-19) has impacted healthcare in an unprecedented way since its emergence in late 2019. Outcomes with COVID-19 infection are worse for solid organ transplant recipients compared with the general population.[6] It is possible that COVID-19 vaccination may lead to immune dysregulation in some solid organ transplant recipients, thereby increasing risks for CMV reactivation.[7] Here, we present 10 cases of CMV infection in solid organ transplant recipients shortly after COVID-19 mRNA vaccination.

CASES

Between March 1, 2021, and June 30, 2021, we identified 10 cases of CMV infection in solid organ transplant recipients within 45 d of COVID-19 mRNA vaccination as summarized in Table 1. Of these, 3 each were lung, heart, and kidney allograft recipients, whereas 1 was a dual heart-kidney allograft recipient. Ages ranged from 32 to 73 y. Indications for organ transplantation are available in the table. Two of the lung transplant recipients, 1 heart recipient, and 1 kidney recipient were CMV high-risk status (donor positive [D+]/recipient negative [R–]), whereas the others were recipient-seropositive (intermediate risk) for CMV. Median time to polymerase chain reaction (PCR) detection of CMV DNAemia from the second dose of mRNA vaccine was 15 d with a range of 4–44 d. The most recent transplant was a heart recipient transplanted 8 mo prior who had come off antiviral prophylaxis at 6 mo posttranplant, whereas the most remote transplant was a heart recipient transplanted 14 y prior. None of these recipients had posttransplant CMV infection detected previously. All patients were off antiviral prophylaxis either because of center or program protocol (available in **Table S1, SDC**, http://links.lww.com/TXD/A429) or because of intolerance of prophylactic medications due to cytopenias, and they were on their standard immunosuppressive regimen at the time of vaccination. Symptoms were variable but ranged from asymptomatic to acute respiratory and multiorgan failure. However, all patients had the resolution of CMV DNAemia

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TABLE 1.

Summary of Solid Organ Transplant Recipients with CMV Reactivation after mRNA COVID-19 Vaccine Administration

Case no.	Vaccine	Age, y	Gender	Type of transplant	Primary disease	Time since transplant	Donor/recipient CMV status (±)	Presenting symptoms	Treatment	Time to serum CMV DNA PCR <200, d	CMV highest serum DNA PCR (IU/mL)
1	mRNA-1273 (Moderna)	63	M	Right lung	IPF	34 mo	(±)	Fever, dyspnea	IV ganciclovir followed by oral valganciclovir	30	164 000
2	mRNA-1273 (Moderna)	70	F	Right lung	IPF	18 mo	(±)	Dyspnea, cough	IV ganciclovir followed by oral valganciclovir	45	175 973
3	BNT162b2 (Pfizer)/ mRNA-1273 (Moderna)	42	M	Bilateral lung	Bronchiectasis	22 mo	(±)	Dyspnea	Oral valganciclovir	42	15 900
4	BNT162b2 (Pfizer)	73	M	Heart and Kidney	Ischemic cardiomyopathy	14 y (heart), 6 y (kidney)	(±)	Asymptomatic	None	14	363
5	BNT162b2 (Pfizer)	53	M	Heart	Nonischemic cardiomyopathy	9 mo	(±)	Fatigue, exertional dyspnea	Oral valganciclovir	16	272
6	mRNA-1273 (Moderna)	56	F	Heart	Nonischemic cardiomyopathy	8 mo	(±)	Asymptomatic	IV ganciclovir followed by oral valganciclovir	16	3969
7	mRNA-1273 (Moderna)	67	M	Heart	Nonischemic cardiomyopathy	18 mo	(+/+)	Asymptomatic	Oral valganciclovir	7	1792
8	BNT162b2 (Pfizer)	32	M	Kidney	IgA nephropathy	10 mo	(+/+)	Asymptomatic	Oral valganciclovir	11	755
9	BNT162b2 (Pfizer)	60	M	Kidney	HIV nephropathy	14 mo	(+/+)	Asymptomatic	Oral valganciclovir	15	1285
10	BNT162b2 (Pfizer)	73	M	Kidney	Diabetic nephropathy	18 mo	(±)	Weakness	IV ganciclovir followed by oral valganciclovir	58	3 110 000

Case no.	Prior CMV infection	COVID antibody	CMV disease state	Admission leukocyte count	Admission absolute lymphocyte count	Immuno suppression	Cessation of prophylaxis mo/y before first CMV vaccine	Episode of Rejection y/n after vaccination	Time from last episode of rejection to + CMV PCR (rejection grade)	Time from COVID-19 vaccination second dose to + CMV PCR, d
1	No	Negative	CMV pneumonitis	2	1.04	Tacrolimus, Mycophenolate 500 mg BID, Prednisone 5 mg	2 mo	N	2 y 6 mo (A2B0)	16
2	No	Negative	CMV pneumonitis	5	0.88	Prednisone 10 mg Tacrolimus	2 mo	N	1 y 2 mo (A2B0)	5
3	No	Negative	CMV Viremia	4	1	Tacrolimus, Mycophenolate 500 mg BID, Prednisone 10 mg	3 mo	N	1 y 9 mo (A2B2R)	4
4	No	Negative	CMV Viremia	5.4	1.35	Tacrolimus, Mycophenolate 500 mg BID, Prednisone 5 mg	4 y	N	4 y (ACR 2016)	30
5	No	Negative	CMV Pneumonitis	8.3	1.01	Tacrolimus, Mycophenolate 500 mg BID, Prednisone 5 mg	4 mo	N	6 mo (ACR 2R)	14
6	No	Negative	CMV Viremia	5.1	2.59	Tacrolimus, Mycophenolate 250 mg BID, Prednisone 5 mg	2 mo	N	N/A	24
7	No	Negative	CMV Viremia	4.9	0.5	Tacrolimus, Mycophenolate 500 TID	2 mo	N	N/A	16
8	No	Negative	CMV Viremia	6.3	0.59	Tacrolimus, Mycophenolate 250 TID	4 mo	N	N/A	44
9	No	Negative	CMV Viremia	3	1.02	Tacrolimus, Mycophenolate 250 mg BID, Prednisone 10 mg	3 mo	N	6 mo (1B)	15
10	No	Negative	CMV Viremia	5.2	0.67	Tacrolimus, Prednisone 10 mg	7 mo	N	N/A	18

BID, twice a day; CMV, cytomegalovirus; F, female; Ig, immunoglobulin; IPF, idiopathic pulmonary fibrosis; IV, intravenous; M, male; PCR, polymerase chain reaction; TID, three times a day.
Case 3 received the 2-dose BNT162b2 vaccine series 8 wk before starting the 2-dose mRNA-1273 series; the reported positive CMV PCR resulted 4 d after completing the mRNA-1273 series.

by the censor date with a range of 7–58 d. Therapy included reduction of immunosuppression, intravenous ganciclovir, and oral valganciclovir. The median peak CMV DNA PCR in the cohort was 1792 IU/ml with a range of 272 to 3.11 million IU/ml.

Three patients received the mRNA-1273 (Moderna) vaccine, whereas the remainder received the BNT162b2 (Pfizer) vaccine. None of the recipients developed immunoglobulin G antibodies to SARS-CoV-2 in response to vaccination. There were no documented cases of COVID-19 in these transplant recipients.

The first identified and representative patient was a 63-y-old man with idiopathic pulmonary fibrosis who underwent right lung transplant (D+/R–) 3 y before COVID-19 vaccination and had been clinically well. His prophylactic valganciclovir was stopped 24 mo after transplant per institutional protocol. After the second dose of the mRNA-1273 vaccine, he developed generalized malaise and a slightly elevated temperature of 37.2 °C (99 °F). Sixteen days after his second vaccine dose, he presented to the emergency department with dyspnea and acute hypoxemia. He underwent bronchoscopy with transbronchial biopsies which demonstrated CMV pneumonitis with no evidence of acute cellular rejection. His admission blood CMV DNA PCR was 164 000 IU/ml. Treatment with intravenous ganciclovir reduced the CMV DNAemia to 69 000 IU/ml within a week. Reduction in CMV viral load was accompanied by clinical improvement. One week after discharge, he required readmission with worsening respiratory failure requiring mechanical ventilation. His CMV PCR was 707 IU/ml, and he was treated for presumed acute cellular rejection with high-dose intravenous corticosteroids with eventual liberation from mechanical ventilation. Two weeks after the second discharge, his blood CMV PCR was <200 IU/ml, and he was transitioned from intravenous ganciclovir to oral valganciclovir.

A second representative case is a 73-y-old man who underwent deceased donor kidney transplantation (D+/R–) the year before vaccination for end-stage renal disease due to diabetes. The patient had an uncomplicated surgical recovery and was clinically well. Two weeks after the second dose of the BNT162b2 vaccine, he presented to the emergency department with generalized weakness, fatigue, hypotension, and elevated serum creatinine (1.6 mg/dL from baseline of 1.1 mg/dL). Blood CMV PCR was 3.11 million IU/mL. He was treated with intravenous ganciclovir with reduction in CMV DNAemia to 41 000 IU/mL after 3 wk. He was transitioned to oral valganciclovir and his blood CMV PCR was 415 IU/mL 1 wk later. The patient remains on prophylactic valganciclovir with undetectable blood CMV DNA PCR.

DISCUSSION

We present 10 cases of CMV DNAemia after COVID-19 mRNA vaccination in solid organ transplant recipients; a phenomenon we believe is underrecognized. Overall, CMV reactivation after vaccination in solid organ transplant recipients appears to be very rare, and to our knowledge there is only 1 published report of 2 cases of CMV DNAemia viremia in kidney transplant recipients after receiving an inactivated influenza vaccine.[8] Our case series is the first to describe CMV DNAemia after COVID-19 vaccination in solid organ transplant recipients. By virtue of its observational nature, our study is unable to draw a causal association between vaccination and CMV infections. However, all cases of CMV DNAemia described in our case series occurred in close temporal relation to patients receiving either the mRNA-1273 or BNT162b2 COVID-19 mRNA vaccines supporting a strong possible role. Notably, all the patients included in this series were not on CMV prophylaxis for at least 2 mo before COVID-19 vaccination (Table 1), with 6 of the 10 patients having had their prophylaxis stopped 3 mo or fewer before vaccination, suggesting these patients were in the high-risk period for reactivation or late CMV infection when they were vaccinated. However, none of these patients had CMV infections between the end of prophylaxis and the occurrence of CMV DNAemia after vaccination. Also, there was no rejection diagnosed in the 2 mo before CMV DNAemia, and thus augmentation of immunosuppression was not a contributing factor to CMV reactivation. Although the risk–benefit assessment strongly favors COVID-19 vaccination in solid organ transplant recipients,[9,10] care teams should consider active monitoring for CMV disease activity in these patients. In some cases, CMV prophylaxis may be warranted depending on patients' risk profiles.

Potential causes of CMV infection following COVID-19 mRNA vaccination may include "immune senescence" or dysregulation of the immune system.[7-12] As patients with latent CMV age, more of their T-cell pool is directed toward keeping CMV latent. Thus, when faced with a novel virus like SARS-CoV-2, the immune system may be unable to appropriately expand the naïve T-cell pool and develop an adequate immune response[13] without compromising immunity geared toward keeping CMV at bay. When patients receive an mRNA vaccine, the T-cell pool may be redirected toward the COVID-19 spike protein and away from CMV suppression. Another hypothesis is that the spike protein itself causes immune activation, thus leading to CMV reactivation. Others have suggested that about 25% of mRNA-vaccinated individuals have circulating spike proteins in their blood upwards of 1 mo after vaccination. As the spike protein is known to drive an inflammatory response, in immunosuppressed folks this phenomenon may drive virus reactivation.[14] Regardless, awareness of this phenomenon is crucial to the management of these patients because of both short- and long-term deleterious consequences of CMV infection.

CMV disease in transplant recipients often requires treatment, sometimes with hospitalization, and carries a risk for chronic allograft dysfunction.[15-17] Moreover, the mortality rate of primary CMV infection 1 y after thoracic organ transplant may be as high as 54%.[18] Although the majority of kidney transplant CMV infections tend to be asymptomatic, they may still result in significant morbidity and mortality.[19] Moreover, treatment of CMV disease can be challenging.

CONCLUSION

CMV infection after COVID-19 vaccination in solid organ transplant recipients may be an underappreciated phenomenon; the risk seems to be highest in the population of patients who recently had their prophylaxis discontinued. Clearly, the risk–benefit assessment strongly favors COVID-19 vaccination for solid organ recipients. However, an increased awareness of a potentially associated risk of CMV reactivation may help care teams to more rapidly diagnose and manage this

complication or perhaps consider short-term reinstitution of viral prophylaxis around the time of vaccination.

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