



Case report

Cytomegalovirus reactivation in critically-ill Coronavirus Disease 2019 patients: A case series of 11 patients



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ABSTRACT

The mortality associated with Coronavirus Disease 2019 is greatly influenced by known risk factors such as elderly age, cardiovascular disease, hypertension, diabetes, and immunosuppression. As cytomegalovirus reactivation in critically ill patients has been linked with higher morbidity and mortality in intensive care settings, it has been suggested that cytomegalovirus reactivation might lead to worse clinical outcomes of patients with Coronavirus Disease 2019. Here we describe the clinical course of 11 patients with Coronavirus Disease 2019 and concomitant cytomegalovirus viremia. We conclude that further research is necessary to formulate guidelines on diagnosis and treatment of cytomegalovirus reactivation in Coronavirus Disease 2019 patients.

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Introduction

Herpesviridae reactivation, especially cytomegalovirus (CMV) reactivation, has been well studied in mechanically ventilated patients in intensive care units (ICU). Studies have shown CMV reactivation rate in critically ill patients varies from 0% to 98% depending on the definition of CMV reactivation and study design [1]. Also, there is strong evidence that suggests an association between CMV reactivation and higher morbidity and mortality in the ICU [1–5]. However, whether to treat CMV reactivation without overt clinical disease remains controversial, and there is no data to guide preemptive treatment approaches in previously immunocompetent ICU patients [1].

Since the emergence of Coronavirus Disease 2019 (COVID-19), CMV reactivation has also been noted in critically ill patients and the question remains if this reactivation could eventually lead to worse outcomes in these patients. In a detailed review, Moss [6] discussed mechanisms by which CMV infection may act to worsen the clinical outcome of COVID-19. Suggested mechanisms include immune-senescence, vascular endothelial damage by CMV, and hyperglycemia-

related CMV-specific T cell response. Kadambari et al. [7] also suggested CMV-induced immune senescence could potentially lead to higher COVID-19 mortality in the elderly and ethnic minority populations.

A French study showed that among 34 patients who are admitted to ICU for COVID-19, 5 patients (15%) had CMV reactivation detected by PCR [8]. In another French study involving 38 patients who were mechanically ventilated longer than 7 days, 9 patients (24%) had CMV reactivation shown by real-time polymerase chain reaction (PCR) on tracheal aspirates [9]. However, both studies failed to show the association between ICU mortality and CMV reactivation. To this date, there is no case series or retrospective observational study in the United States describing clinical courses of patients who were critically ill with COVID-19 and had CMV reactivation.

In our case series, we report 11 cases of patients who required noninvasive ventilation or mechanical ventilation secondary to COVID-19 pneumonia and had PCR confirmed CMV viremia. Electronic medical records of patients admitted to Memorial Healthcare System hospitals (Memorial Hospital West, Memorial Hospital Miramar, Memorial Regional Hospital) from June 1st, 2020 to August 31st, 2021 were reviewed. All patients had SARS-CoV-2 infection confirmed with oropharyngeal and/or nasopharyngeal swab PCR. Patients with CMV viral load higher than 500 IU/mL were included in the review. The study protocol was approved by the Institutional Review Board of Memorial Healthcare System.

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Table 1
Baseline characteristics.

Case number	Age (years)	Sex	BMI at admission (kg/m ²)	Smoking status	Vaccination status	Comorbidities and immunosuppressants
Case 1	53	F	34.4	Never smoker	None	Asthma
Case 2	53	F	31.0	Never smoker	None	Type 2 diabetes mellitus
Case 3	77	M	28.1	Never smoker	None	Chronic lymphocytic leukemia, hypertension
Case 4	62	M	28.9	Never smoker	None	Type 2 diabetes mellitus, hyperlipidemia
Case 5	59	F	35.5	Never smoker	None	Asthma, hypertension
Case 6	48	F	34.8	Never smoker	None	Pulmonary fibrosis, rheumatoid arthritis (on prednisone, rituximab, leflunomide), history of pulmonary embolism, Type 2 diabetes mellitus, hyperlipidemia, hypertension, hypothyroidism
Case 7	58	F	38.1	Never smoker	None	Type 2 diabetes mellitus, hypertension
Case 8	67	M	25.1	Never smoker	None	None
Case 9	63	M	24.5	Never smoker	None	Type 2 diabetes mellitus, hypertension, Hyperlipidemia
Case 10	51	M	32.5	Never smoker	None	None
Case 11	64	M	37.0	Never smoker	None	Congestive heart failure, Type 2 diabetes mellitus, hypertension, coronary artery disease, hyperlipidemia

Results

We conducted a retrospective electronic medical chart audit of patients with CMV viremia above 500 IU/mL and COVID-19 pneumonia from June 1st, 2020 to August 31st, 2021. 11 cases were identified. [Table 1](#) identifies the baseline characteristics of 11 cases. The mean age was 59.54 years with a median of 59 years. The case series included 5 females and 6 males who had an average body mass index (BMI) of 31.80 kg/m². All 11 patients were never-smokers and unvaccinated against SARS-CoV-2. We did not identify any particular comorbidity that pointed to an increased risk of CMV reactivation in our patients. Type 2 diabetes mellitus was seen in 6 out of the 11 patients. Of note, case 3 had a history of chronic lymphocytic leukemia and case 6 had a history of rheumatoid arthritis and idiopathic pulmonary fibrosis.

[Table 2](#) highlights the correlation between CMV viremia and COVID-19 in the context of specific treatments offered for both diseases. The average peak CMV viral load of all 11 patients was 188,393.09 IU/mL with a median of 23,985 IU/mL. All 11 patients received at least 1 dose of convalescent plasma with cases 1 and 6 receiving an additional second dose. All 11 patients were treated with remdesivir; 8 out of 11 received the extended therapy dosing regimen of more than 5 days with the patient in case 10 receiving only 4 days. 4 out of 11 patients received a dose of tocilizumab. All patients in our case series received a prolonged course of intravenous corticosteroids. The average days from the initial positive SARS-CoV-2 PCR to serum CMV viral load above 500 IU/mL was 53.82 days with a median of 51 days. All but 2 of the patients who had clinically significant CMV viremia received treatment with IV ganciclovir and only case 1 required CMV-IVIG in addition to ganciclovir due to severely elevated viral load. Only 1 patient (case 3)

had tissue invasive CMV disease in the form of hemorrhagic esophagitis.

10 patients required mechanical ventilation under ICU care. Their average length of stay in ICU was 64.9 days (median 58.5 days). 3 out of 11 patients were placed on extracorporeal membrane oxygenation (ECMO) therapy. 9 out of 11 patients (81.8%) died during their hospital stay. Case 1 was transferred to an acute rehabilitation facility and case 3 who did not require an ICU stay was discharged home. [Table 3](#).

Discussion

This study demonstrates that it is not uncommon to have CMV reactivation with a prolonged course of severe illness secondary to COVID-19 pneumonia. As described in the result section, patients included in this study were critically ill, most of them requiring mechanical ventilation and 27.3% (3/11) requiring ECMO. The outcome among these patients was poor, 81.8% (9/11) died during hospitalization. These findings suggest severe illness due to COVID-19 infection is a sufficient driver for CMV reactivation. In addition, the immunosuppressive effect of corticosteroids might have played a role in CMV reactivation. However, given clinical evidence behind benefits of corticosteroids in patients with COVID-19 pneumonia [10], it is difficult to advocate against the use of corticosteroid despite the increased risk of opportunistic infections such as CMV.

Whether CMV reactivation and/or treatment for CMV reactivation significantly changes clinical course is yet unclear. 90.9% (10/11) received treatment in the form of ganciclovir and/or CMV-IVIG. In all patients who received CMV-specific treatment, serum viral load decreased in follow-up PCR studies in response to the treatment. Specifically, it is notable that only case 1 received CMV-IVIG and it is one of the two survivor cases in our case series. However due to the

Table 2
COVID-19 and CMV diagnosis and treatment.

Case number	SARS-CoV-2 diagnosis date	Tocilizumab treatment	Convalescent plasma treatment	Remdesivir treatment (days)	SARS-CoV-2 + to CMV+ days	Peak CMV viral load (IU/mL)	Ganciclovir treatment	CMV-IVIG treatment
Case 1	8/4/2020	No	Yes, 2 doses	10	83	359,802	Yes	Yes
Case 2	4/7/2021	No	Yes, 1 dose	15	49	524	Yes	No
Case 3	1/12/2021	No	Yes, 1 dose	5	35	1,116,362	Yes	No
Case 4	9/22/2020	No	Yes, 1 dose	10	37	24,691	Yes	No
Case 5	7/24/2020	Yes	Yes, 1 dose	10	53	239,337	Yes	No
Case 6	4/1/2021	Yes	Yes, 2 doses	5	51	23,985	Yes	No
Case 7	1/19/2021	No	Yes, 1 dose	10	58	23,177	Yes	No
Case 8	7/10/2020	Yes	Yes, 1 dose	10	85	248,966	Yes	No
Case 9	8/17/2020	No	Yes, 1 dose	10	42	20,295	Yes	No
Case 10	1/15/2021	Yes	Yes, 1 dose	4	61	1328	No ^a	No
Case 11	7/2/2021	Yes	Yes, 1 dose	10	38	13,857	No	No

^a Not given due to worsening thrombocytopenia.

Table 3
ICU statistics.

Case number	ICU length of stay (days)	Ventilated days	COVID+ to CMV+ days ^a	ECMO dependent days	Outcome on discharge
Case 1	142	107	83	44	Transferred to Acute Rehab Facility
Case 2	66	66	49	0	Deceased
Case 3	0	0	35	0	Discharged Home
Case 4	40	40	37	0	Deceased
Case 5	67	67	53	0	Deceased
Case 6	57	46	51	41	Deceased
Case 7	47	9	58	0	Deceased
Case 8	90	73	85	0	Deceased
Case 9	60	58	42	0	Deceased
Case 10	40	43	61	38	Deceased
Case 11	40	40	38	0	Deceased

^a Days from first positive SARS-CoV-2 PCR to serum CMV viral load above 500 IU/mL.

limited number of cases, the correlation between CMV-specific treatment, viral load reduction, and clinical outcomes remains unclear. To better understand the effect of treatment, we suggest clinical trials that compare the clinical outcomes between different antiviral treatments: ganciclovir or foscarnet, with or without addition of CMV-IVIG.

CMV reactivation can lead to not only viremia but also tissue-invasive diseases, such as pneumonitis, colitis, esophagitis, encephalitis, and retinitis. In patients critically ill with COVID-19 pneumonia, it is practically difficult to make a diagnosis of CMV tissue-invasive disease for the following reasons. The gold standard for diagnosis of CMV invasive disease is to obtain tissue biopsy for histologic examination and/or tissue PCR. However, it is often not feasible to perform transbronchial biopsy in severely ill COVID-19 patients due to their tenuous respiratory status and risk of provoking pneumothorax. Similarly, with regard to diagnosis of invasive gastrointestinal tract disease, clinical decisions are often made not to pursue endoscopy or colonoscopy in critically-ill COVID-19 patients as risks outweigh benefits.

Our study also suggests that COVID-19 severity does not correlate well with CMV viral load or severity of CMV disease. In our case series, only one patient (case 3) had biopsy-proven tissue-invasive CMV disease, which was hemorrhagic esophagitis. The patient had a history of stage 0 chronic lymphocytic leukemia (CLL) and was admitted with COVID-19 pneumonia. He required supplemental oxygen via high flow nasal cannula (HFNC) and was discharged home. He presented 2 days later with melena and was diagnosed with CMV hemorrhagic esophagitis via esophagogastroduodenoscopy (EGD) and biopsy. He was successfully treated with a 3-week course of ganciclovir. It is also noteworthy that case 3, who survived and was discharged to home, had the earliest detection of CMV reactivation at 35 days since positive SARS-CoV-2 PCR out of all the patients in our case series. This observation raises further research questions as if early detection and initiation of CMV-specific treatment would lead to better prognosis.

While the benefit of treatment for CMV viremia without diagnosis of tissue-invasive disease remains unclear, there exists risk of adverse effects from antiviral medication. Toxicity of ganciclovir includes granulocytopenia, anemia, thrombocytopenia, pancytopenia, and acute kidney injury. CMV-IVIG can cause adverse effects such as anaphylaxis/hypersensitivity reactions, aseptic meningitis, hemolysis, pulmonary edema, renal impairment, and thrombotic events. As guidelines for treatment of CMV reactivation in non-transplant critically ill patients are not well established, we argue that risks and benefits should be carefully considered when treating CMV viremia in critically ill patients with COVID-19 pneumonia.

In this case series, CMV PCR was ordered in critically-ill COVID-19 patients with deteriorating clinical courses, such as increasing demands for oxygenation on a mechanical ventilator, increasing vasopressor requirements, or new-onset fever. However, this was not the standard of care and decisions for diagnostic testing were made

based on individual clinician's judgment rather than specific criteria. It is unclear when diagnostic study for CMV reactivation should be pursued in patients with COVID-19 in critical status in the absence of supporting symptoms of invasive CMV disease.

In summary, in a critically ill patient with COVID-19 infection, reactivation of CMV is often observed, and some cases can lead to clinically overt disease. Also, our case series reflected a high mortality in COVID-19 patients with CMV viremia. However, it is unknown if this association is clinically relevant or incidental. In addition, further research is required to explore the answer to these questions; do patients with COVID-19 pneumonia experience higher rate of CMV reactivation than patients who are critically ill from other etiologies, when should a clinician test for CMV viremia, what should be the threshold to define clinically significant CMV viremia, and whether treating CMV viremia improves morbidity and mortality.

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Ethical disclosures

The Institutional Review Board (IRB) at the corresponding author's institution approved the case series. Informed consent was waived by the IRB.

Consent

The Institutional Review Board (IRB) at the corresponding author's institution approved the case series. Informed consent was waived by the IRB.

CRediT authorship contribution statement

Myeongji Kim: Investigation, Resources, Data curation, Writing – original draft, Project administration. **Jeffy Jacob:** Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Daniel Mayer:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Paula Andrea Eckardt:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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None.

Conflict of interest

The authors declare that they don't have any conflict of interest that should be disclosed.

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