



Cytomegalovirus Reactivation in Critically-ill COVID-19 Patients

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To the Editor,

COVID-19 is an ongoing global pandemic that causes significant morbidity and mortality. Although severe pneumonia and acute respiratory distress syndrome (ARDS) are seen in the foreground, it causes widespread diseases, involving multiple organ systems in severe cases. Various immunosuppressive agents, such as corticosteroids and interleukin antagonists, are used in the treatment of COVID-19. Thus, immune paralysis due to severe COVID-19, sepsis, and drugs used for its treatment cause secondary bacterial/fungal infections and viral reactivation.¹

Cytomegalovirus (CMV) reactivation occurs in 30% of immunocompetent patients with ARDS and is associated with increased mortality. CMV reactivation is important because it causes prolonged invasive mechanical ventilation, increases the incidence of secondary infections, prolongs intensive care unit (ICU) stay, and increases the mortality rate.²

However, there is a paucity of data on CMV infections in critically-ill patients with COVID-19. Therefore, we retrospectively evaluated the outcomes and clinical characteristics of CMV reactivation cases in our COVID-19 patients.

Patients who were admitted to our pandemic ICU between March 2020 and May 2021 were evaluated retrospectively, and those with a CMV viral load higher than 500 copies/mL were included in the study.

Out of 218 SARS-CoV-2 PCR positive ICU patients, 10 patients with CMV viral loads of >500 copies/ml were identified. CMV viral tests (NeuMoDx, USA) were not performed routinely in our ICU. It was performed only if there was a suspicion of reactivation, such as nonbacterial pneumonia or decreased white blood cell and platelet counts in this patient group. The mean age of our study participants was 67.7 (53-84) years, and six of them were males. The most common comorbidities were hypertension (6/10) and atherosclerotic heart disease (5/10). Nine patients received

corticosteroids. An interleukin-1 receptor antagonist (Anakinra) and corticosteroids were used in four patients. All patients required invasive mechanical ventilation. All patients (except one) were diagnosed with severe ARDS ($pO_2/FiO_2 < 100$) on admission. Seven patients died and three patients were discharged from the ICU. CMV PCR positivity was detected on the third day of ICU admission (at the earliest) and the 35th day (at the latest) with a mean period of 24 days. Table 1 summarizes patients' characteristics. All patients in this case series were administered standard CMV viremia treatment with ganciclovir or valganciclovir.

Although coinfection with CMV is frequent in critically-ill patients due to underlying immunosuppression of multiple causes, its impact on COVID-19 patients remains unclear. Studies on CMV reactivation are mostly in the form of case reports, and it is remarkable that in some of the cases, the findings leading to the diagnosis are primarily gastrointestinal complaints.³⁻⁵

When the characteristics of our COVID-19 patients were examined, CMV reactivation was observed in both young and old patients; in a patient without any comorbid disease, and in a patient who had received neither corticosteroids nor an interleukin antagonist. The fact that CMV reactivation has been encountered in patients with such a wide range of characteristics has led people to think that significant awareness is required in this regard.

The role of the SARS-CoV-2 infection on CMV reactivation is not yet clear. In patients with severe COVID-19, multiple factors such as secondary immune paralysis due to critical illness itself, the presence of multiple comorbidities, underlying immunosuppressive treatments, or immunomodulatory treatments may be in effect. As for the immunomodulatory treatments, corticosteroids and interleukin antagonists are known to be associated with CMV reactivation. To avoid missing the reactivation, routine CMV DNA testing at certain intervals might be an option, especially in high-risk patients.



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TABLE 1. Baseline Demographic and Clinical Characteristics of Patients

	Age	Sex	Comorbidities	Steroid therapy	Immunomodulatory therapy	IMV	Admission pO ₂ /FiO ₂ ratio	Length of ICU stay	ICU mortality
Case 1	57	Male	DM, lung cancer	Dexamethasone 6 mg/day	Anakinra	Yes	54	27	Exitus
Case 2	53	Female	Renal transplantation	Prednisolone 80 mg/day	Anakinra	Yes	110	38	Alive
Case 3	63	Male	HT, CAD	Prednisolone 80 mg/day	Anakinra	Yes	51	24	Exitus
Case 4	67	Male	HT, CAD	Prednisolone 80 mg/day	-	Yes	46	33	Exitus
Case 5	68	Male	CAD, hepatic transplant	Prednisolone 80 mg/day	-	Yes	64	41	Exitus
Case 6	78	Male	-	Prednisolone 80 mg/day	Anakinra	Yes	73	33	Exitus
Case 7	80	Male	HT, CAD	Prednisolone 80 mg/day	-	Yes	57	51	Exitus
Case 8	54	Female	DM, HT, renal transplant	Dexamethasone 6 mg/day	-	Yes	84	41	Alive
Case 9	84	Female	HT, CAD	-	-	Yes	67	14	Alive
Case 10	73	Female	HT, CAD, asthma, obesity	Prednisolone 160 mg/day	-	Yes	230	44	Exitus

ICU, Intensive care unit; IMV, invasive mechanical ventilation; DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease

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