



Severe, Progressive Meningoencephalitis in a Patient with Coexisting SARS-CoV-2 and Cytomegalovirus Infection: A Case Report

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Received 2022 March 29; Accepted 2022 August 30.

Abstract

SARS-CoV-2, the pathogen responsible for COVID-19, has infected hundreds of millions since its emergence in late December 2019. Recently, concern has been raised due to the increased prevalence of co-infections with opportunistic pathogens among these patients. Though not common, co-infections may be associated with adverse outcomes and increased risk of morbidity and mortality among patients suffering from COVID-19. Cytomegalovirus (CMV) infection is a serious problem among immunocompromised and critically ill patients. So far, few cases of co-infection with COVID-19 and CMV have been reported. Here, we report the co-infection with COVID-19 and CMV in a young woman presenting with sudden, progressive fever, delusion, agitation, bizarre behavior, seizure, and loss of consciousness leading to death despite receiving appropriate anti-viral treatment. To the best of our knowledge, this is the first case of coexisting SARS-CoV-2 and CMV infection presenting with severe, progressive meningoencephalitis in the era of COVID-19.

Keywords: Cytomegalovirus, SARS-CoV-2, COVID-19, Meningoencephalitis, Co-infection

1. Introduction

Since its emergence in December 2019 in Wuhan, China, COVID-19 has infected more than 237 million individuals and caused more than 4 million deaths (1). Patients with SARS-CoV-2 infection are at an increased risk of superinfection with various pathogens, including bacteria, fungus, and viruses such as *Streptococcus pneumoniae*, *Streptococcus aureus*, influenza A virus, *Aspergillus fumigatus*, and *Candida albicans* (2). Superinfection among patients suffering from infection with SARS-CoV-2 is associated with increased severity of disease, prolonged hospitalization, and a higher rate of mortality (2). Up to now, a few cases of co-infection with SARS-CoV-2 and cytomegalovirus (CMV) have been reported (3-5). However, the majority of them presented with gastrointestinal symptoms, and no case of co-infection with COVID-19 and CMV presenting with meningoencephalitis has been reported. Here, we describe a case of coexisting COVID-19 pneumonia and CMV meningoencephalitis.

2. Case Presentation

A 27-year-old woman was referred to our emergency department with a history of fever, headache, delusion, agita-

tion, bizarre behavior, and sudden, progressive loss of consciousness from one day before admission. No history of respiratory symptoms was reported. Her family members denied any previous episodes of altered consciousness or abnormal behavior. The patient had no history of underlying medical issues. There was no history of inherited or acquired immunodeficiency diseases. Any history of smoking, drug abuse, or alcohol consumption was denied.

At the time of admission, the patient was confused with a Glasgow Coma Scale (GCS) of 10/15. In vital sign measurement, the blood pressure was 100/60 mmHg, respiratory rate 16/minute, heart rate 72 beats per minute (bpm), oral temperature 37.1° centigrade, and O₂ saturation 97% while the patient was breathing ambient air. In head and neck physical examination, pupils were 2 mm in size and equally reactive to light. No neck stiffness was found, and tendon reflexes were normal. Lung auscultation revealed bilateral basal crackles. Other findings during the physical examination were normal. At admission, the blood test revealed a white blood cell count of 7000/ μ L, hemoglobin of 13.1 g/dL, platelet count of 107000/ μ L, and serum iron of 63 μ g/dL. Biochemical analysis was normal except for a slight increase in the level of liver enzymes with an aspartate transaminase of 35 U/L, alanine transaminase of 41

U/L, and alkaline phosphatase of 258 U/L. Venous blood gas analysis showed a pH of 7.41, PCO_2 of 24.9 mmHg, and HCO_3 of 20.1. In addition, a urine drug screening was conducted, which showed negative results.

Due to fever and lung crackles, a spiral lung computed tomography (CT) scan was performed, showing ground-glass opacities in the posterior segment of both lungs' right upper lobe and basal segments. A subsequent SARS-CoV-2 polymerase chain reaction (PCR) test was performed, which was positive. Thus, the diagnosis of COVID-19 infection was confirmed, and treatment was initiated based on the national protocol for the treatment of COVID-19 (6).

On the second day of hospitalization, she suddenly developed a tonic-clonic seizure and dropped her GCS to 7/15. In physical examination after the seizure, pupils were dilated with a slight reaction to light, and deep tendon reflexes were increased. Pulse oximetry revealed an O_2 saturation of 90% with a nasal mask. Treatment with antiepileptic drugs, including diazepam and levetiracetam, was initiated; however, episodes of seizure-like movements were repeated. Thus, maintenance treatment with phenytoin was started. As the patient continued to have tonic-clonic seizures despite receiving appropriate antiepileptic drugs, she was intubated and transferred to the intensive care unit (ICU). After a few hours of seizures, she suddenly developed tachycardia, and her heart rate raised to 180 bpm. Electrocardiography was performed, which demonstrated atrial tachycardia; thus, treatment with adenosine and verapamil was started. After one hour, no decrease in the patient heart rate occurred; therefore, metoprolol was added to the drug regimen to control heart rate, which resulted in a decreased heart rate to 160 bpm.

Bedside echocardiography was also performed, which revealed no abnormal findings. The patient's heart rate gradually decreased due to treatment; however, she still remained tachycardia with a heart rate of more than 100 bpm. A blood test was performed, which revealed an increased white blood cell count ($21500/\mu\text{L}$), thrombocytopenia (platelet count of $76000/\mu\text{L}$), and severe lymphopenia (5.6%). Furthermore, the biochemical analysis showed serum creatinine of 1.9 mg/dL, urea of 38 mg/dL, sodium of 149 mEq/L, and creatine phosphokinase (CPK) of 2491 U/L. Based on urine analysis, a protein of 1+, glucose of 1+, blood of 2+, WBC of 2 - 4, and RBC of 20 - 25, as well as granular casts, indicate acute renal failure. Thus, the patient underwent invasive intravenous fluid therapy.

Due to seizure and altered state of consciousness, a brain CT scan was done, which demonstrated soft tissue swelling in the right parietal and left occipital region and a decreased contrast between white matter and gray matter, suggesting diffused brain edema. Further, due to extensive cerebral edema, a brain CT angiography was performed, which showed meningeal enhancement and bilateral infarction of the posterior cerebral, posterior tempo-

ral, and top of the basilar artery. No evidence of occupying the lesion was found. Thus, the diagnosis of meningoencephalitis was confirmed, and empirical treatment with acyclovir was started on the third day of hospitalization. Subsequently, the patient underwent a lumbar puncture which revealed clear and colorless cerebrospinal fluid (CSF) under normal pressure. In the biochemical analysis of CSF, lactate of 31 mg/dL, protein of 79 g/dL, LDH of 45 U/L, and sugar of 135 mg/dL were noted. Furthermore, the CSF cell count was normal. cerebrospinal fluid culture was sterile, and no pathogenic bacteria, fungus, or tuberculosis was detected. Moreover, a PCR test was conducted, which was positive for CMV. In CSF, PCR for herpes simplex viruses, Epstein-Barr virus, varicella-zoster virus, enterovirus, and human herpesviruses were negative. As the diagnosis of CMV meningoencephalitis was confirmed, acyclovir was discontinued, and treatment with ganciclovir was started.

Serial brain CT scans were performed to follow up on pathological changes. On the fourth day of hospitalization, a contrast-enhanced CT scan was carried out, revealing diffused cerebral edema and increased soft-tissue edema in the occipital region.

In addition, on the eighth day of hospitalization, another brain CT scan was performed, which showed soft tissue swelling in the left lateral orbit and frontal region, severe diffuse brain edema, and sulcal effacement. Despite receiving appropriate anti-viral treatment and supportive therapy, the patient's clinical condition deteriorated during hospitalization. Her GCS gradually dropped to 3/15. The levels of O_2 saturation decreased to 80% despite invasive mechanical ventilation. Further lab tests revealed a significant decrease in hemoglobin (6 g/dL) and platelet count ($40000/\mu\text{L}$), which showed no improvement despite blood transfusion. No evidence of upper or lower gastrointestinal bleeding and no external bleeding site was found. Her blood pressure decreased to 80/50 mmHg with no significant response to fluid therapy, and she remained hemodynamically unstable. Serum creatinine, urea, CPK, and sodium levels continued to rise, reaching 2.9 mg/dL, 75 mg/dL, 2583 U/L, and 156 mEq/L on the last day of hospitalization, respectively. The last spiral lung CT scan revealed diffuse ground-glass opacities, basal nodular infiltrations, and subpleural consolidations of both lungs, suggesting COVID-19 pneumonia complicated with aspiration pneumonia. Unfortunately, the patient died on the 13th day of hospitalization due to acute respiratory distress syndrome, septic shock, and multi-organ failure.

3. Discussion

To the best of our knowledge, this is the first case of coexisting SARS-CoV-2 and CMV infection presenting with severe, progressive meningoencephalitis in the era of

COVID-19. Viral co-infections are not common among patients with COVID-19. A recent meta-analysis showed that the prevalence of viral co-infection among adult patients with COVID-19 was almost 2%, with the respiratory syncytial virus as the most common and CMV as the least common viral pathogen (7). Also, another study reported that among 243 patients co-infected with COVID-19 and respiratory pathogens, CMV accounted for only 1.2% of all cases of co-infection (8). Co-infection may be associated with poorer prognoses and worse outcomes (8). It has been shown that CMV co-infection is associated with prolonged hospitalization, a higher length of mechanical ventilation, and an increased mortality rate among infected individuals (9). Until now, only a few cases of co-infection with COVID-19 and CMV have been reported, and most of them suffered gastrointestinal symptoms (4, 5, 10). To the best of our knowledge, this is the first case of fatal CMV meningoencephalitis in a patient with COVID-19 pneumonia.

Cytomegalovirus is a viral pathogen with a double-stranded DNA genome that belongs to the *Herpesviridae* family (11). Almost 50% - 80% of people worldwide have CMV, but it remains clinically non-significant until the individuals become immunocompromised (12). In the immunocompetent state, the virus usually remains latent, and its replication is controlled (13). In contrast, immunosuppression puts the individual at a higher risk of CMV infection/reactivation. Thus, CMV infection/reactivation is more prevalent among immunocompromised patients; however, the prevalence of this infection has increased among immunocompetent patients during recent decades (14). Infection with CMV can affect almost every body organ and may present as retinitis, pneumonia, hepatitis, colitis, meningitis, and encephalitis (14). Cytomegalovirus meningoencephalitis is a rare condition with a significantly higher prevalence among immunocompromised patients and is associated with a poor prognosis (15, 16). Patients with CMV meningoencephalitis may present with a broad spectrum of symptoms, ranging from mild fever and headache to nerve paralysis, coma, and death (14, 15). Our patient, suffering from co-infection with COVID-19 and CMV, also presented with fever and progressive neurological symptoms, including headache, altered consciousness, seizure, and coma leading to death.

Several factors have been known to be associated with an increased risk of CMV co-infection. A study carried out by Al-Omari et al. reported that disturbance in immune system function, undergoing mechanical ventilation, developing sepsis, and critical illness are among the major risk factors associated with an increased risk of CMV infection (17). Most patients with SARS-CoV-2 infection experience some disturbances in their immune system function. For instance, lymphopenia is a common complication among patients suffering from COVID-19, which is associated with the impairment of cellular and humoral im-

mune system function. Since immunocompromised patients are at an increased risk of developing CMV infection, lymphopenia may increase the risk of CMV infection/reactivation among patients with COVID-19. On the other hand, some of the drugs used for the management of COVID-19, such as interleukin 6-antagonists and corticosteroids, are immunosuppressive agents which disturb the normal function of the immune system and increase patient susceptibility to opportunistic infection (10, 12). Moreover, individuals with severe COVID-19 suffer from a critical illness which puts them at a higher risk of CMV infection (18). A meta-analysis showed that CMV infection and reactivation prevalence among critically ill patients were 27% and 31%, respectively (19). After being hospitalized for two days, the patient developed severe COVID-19 and lymphopenia. Further, she underwent invasive mechanical ventilation due to decreased consciousness and O₂ saturation. These factors together might increase the risk of CMV co-infection in this patient.

Several serological and molecular methods have been developed for diagnosing CMV infection. Polymerase chain reaction is a helpful diagnostic method used for detecting the CMV genome in CSF which has a sensitivity of almost 80% and a specificity of 95% (15). Detection of CMV DNA in CSF is considered a clinical marker for diagnosing CMV meningoencephalitis. Since the PCR test performed for our patient was positive for CMV, the diagnosis of CNS infection with the virus was confirmed, and anti-viral therapy was started. The best-known anti-viral drugs for treating CMV infection include a nucleoside analog and a pyrophosphate analog, named ganciclovir and foscarnet, respectively (15). Some studies showed a lack of desirable response to treatment of CMV meningoencephalitis (15). However, the same efficacy of the abovementioned drugs alone or in combination in managing CMV meningoencephalitis is not fully understood. Treatment with ganciclovir was started for our patient once the diagnosis of CMV meningoencephalitis was confirmed. However, no significant response to anti-viral therapy was detected, and the patient's clinical situation deteriorated gradually. Some studies reported that the prognosis of CNS infection with CMV is usually poor, and the patient's survival is less than a few weeks (15). In our case, death occurred during the first 13 days of neurological symptom presentation. In contrast, a study carried out by Rafailidis et al. reported no death among patients suffering from CNS infection with CMV (14). Thus, the prognosis of CNS infection with CMV and the efficacy of available anti-viral treatments should be further elucidated.

Although not common, co-infection with CMV is associated with a poor prognosis, and its prevalence is rising among individuals suffering from COVID-19. Critical illness, immunosuppression, and mechanical ventilation are among the major risk factors increasing the risk of

CMV co-infection and should be considered among COVID-19 patients. Deteriorating the patient's clinical situation or developing uncommon symptoms should raise the clinician's concern for suspicious CMV co-infection, especially in intensive unit care. Early diagnosis and treatment of CMV co-infection may improve the patient's prognosis and survival. Since the rate and outcomes of CMV co-infection in patients suffering from COVID-19 are not fully understood, further research is needed to clarify this issue.

3.1. Conclusions

Patients with COVID-19 are at an increased risk of co-infection with opportunistic pathogens. Critical illness, immune disturbance, and receiving immunosuppressive drugs are among the major factors which increase the risk of co-infection among patients with COVID-19. The suspicion threshold for co-infection with microbial pathogens should be reduced among these individuals, especially those with critical illnesses who suffer lymphopenia, undergo mechanical ventilation, and receive immunosuppressant drugs. Although superinfection is associated with worse outcomes, early diagnosis and treatment may be life-saving. Since co-infection with CMV is not common, it may be underdiagnosed and underestimated in patients suffering from COVID-19, increasing the risk of mortality among these patients. Awareness of presenting symptoms and clinical management of CMV co-infection is necessary for clinicians to diagnose and treat the disease and reduce the risk of further morbidity and mortality among patients with COVID-19.

Footnotes

Authors' Contribution: M. A. M. and Z. T. participated in designing the study. Z. T. and N. P. M. participated performed the acquisition of data and drafting of the manuscript. M. A. M. critically revised the manuscript and supervised the study. All authors carefully read and approved the final manuscript.

Conflict of Interests: The authors declare no conflict of interests.

Data Reproducibility: The authors guarantee that data of the study are available and will be provided if anyone needs them.

Funding/Support: The authors declare no funding/support.

Informed Consent: The authors confirm that patient's family members have signed an informed consent document before manuscript submission.

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