Case Report

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TANAFFOS

Successful Treatment of Encephalitis Following SARS-Cov-2 Infection: A Case Report

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Background: The SARS-CoV-2 invades the cells by attachment of virus spike proteins (S1, S2) to cell membrane and engages angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the epithelium of cerebral vasculature. Here, we describe a patient with encephalitis following SARS-CoV-2 infection.

Case presentation: A 77-year-old male patient presented with mild cough and coryza lasting for eight days without a prior history of underlying disease or neurologic disorder. Oxygen saturation ($SatO_2$) was decreased and behavioral changes, confusion, and headaches were started within three days prior to admission. Bilateral ground glass opacifications and consolidations were noted on chest CT scan. Lymphopenia, highly elevated D-Dimer and ferritin were noted in laboratory results. Brain CT and MRI showed no changes regarding encephalitis. Cerebrospinal fluid was collected as the symptoms persisted. The results of SARS-CoV-2 RNA RT-PCR from CSF and nasopharyngeal samples were positive. The combination therapy with remdesivir, interferon beta-1alpha and methylprednisolone was started. Due to deterioration of the patient's status and $SatO_2$, he was admitted to the ICU and intubated. Tocilizumab, dexamethasone, and mannitol were started. The patient was extubated on the 16th day of ICU admission. The patient's level of consciousness and $SatO_2$ were improved. He was discharged from the hospital a week later.

Conclusion: RT-PCR of CSF sample along with brain imaging can help with diagnosis when encephalitis due to SARS-CoV-2 is suspected. However, no changes regarding encephalitis may be seen on brain CT or MRI. Combination therapy with antivirals, interferon beta, corticosteroids, and tocilizumab can help patients recover in these conditions.

Key words: Encephalitis; COVID-19; SARS-CoV-2; Treatment; Drowsiness

INTRODUCTION

By January 2020, a series of pneumonia caused by novel coronavirus was reported from China. Afterward, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was considered the cause of novel Coronavirus Disease 2019 (COVID-19) (1). The clinical manifestations of COVID-19 mostly include fever, myalgia, arthralgia, cough (productive or non-productive), headaches, mild to severe dyspnea, hypoxia, nausea/vomiting, and diarrhea (2). The SARS-CoV-2 invades the cells via plasma membrane fusion or endosomes. This action is mediated by attachment of virus spike proteins (S1, S2) to cell membrane and engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor. Further, SARS-CoV-2 can cause downregulation of ACE2 from cell surface, which in turn increases

angiotensin II (Ang II) concentration. High concentration of Ang II in pulmonary tissue is responsible for increased vascular permeability, neutrophil infiltrations, and pulmonary edema, which exacerbate acute lung injury (3, 4).

The ACE2 is highly expressed not only in the lungs and intestines but also in the epithelium of cerebral vasculature. Based on animal model studies, SARS-CoV-2 can invade the olfactory bulb, then spread to intracranial components (5-7). Another hypothesis explained that coronaviruses invade the peripheral-nerve terminals, then ascend to the central nervous system (CNS) by trans-synaptic exchanges (8). Following SARS-CoV-2 neuroinvasion, the patient may experience anosmia, headaches, and deterioration of consciousness due to ischemic stroke, intracranial hemorrhage, or encephalitis (9). Here, we present a case of an old patient who presented with behavioral changes, delirium, and severe confusion. The interesting thing about this case was neurological symptoms dominated over the classical symptoms regarding SARS-CoV-2 infection.

CASE SUMMARIES

A 77-year-old male patient presented on the 8th day of illness with mild cough and coryza started on 25 November 2020 without fever and dyspnea. No prior history of hypertension, diabetes, and neurological disorders was noted. The patient had no history of taking any medications or opioid drugs. Also, no history of central nervous system trauma or surgery was reported. On arrival, the blood pressure was 120/70 mmHg, pulse rate was 110/min, temperature was 37.2 ˚C, and oxygen saturation ($SatO_2$) was 90%. Behavioral changes started within three days prior to the admission. The patient was significantly confused, with some degree of drowsiness, headaches, and disorientation to time and place. The neurologic examination was unremarkable. There was no seizure, neck stiffness, or sign of papilledema by ophthalmoscopy. No specific abnormalities were found on abdominal and chest examination.

Spiral chest computed tomography (CT) showed multifocal bilateral patchy ground glass opacifications and consolidations that were highly suggestive of COVID-19 (Figure 1). There was no focal lesion or abnormality in the brain CT scan. Also, no calcification and hemorrhage were observed (Figure 2). Further, brain magnetic resonance imaging (MRI) was obtained. The data from the brain MRI did not show any change regarding encephalitis (Figure 3).

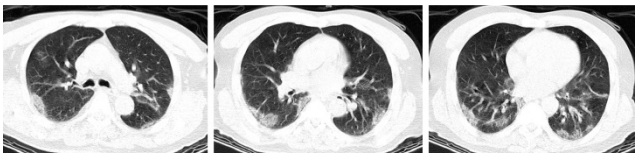

Figure 1. Chest CT-scan showed bilateral ground-glass opacifications and consolidations.

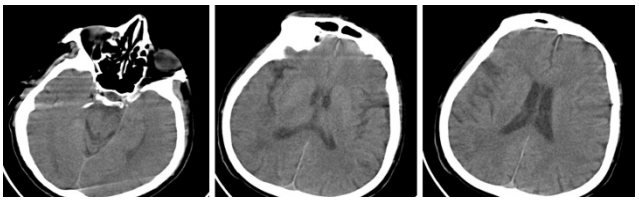

Figure 2. Brain CT-scan.

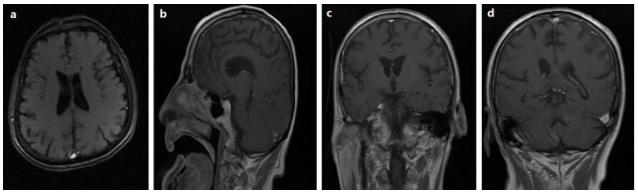

Figure 3. Axial flair (a) and T1-weighted (b-d) MRI at sagittal and coronal view. No changes were observed regarding to encephalitis, ischemia, or hemorrhage.

Primary laboratory findings revealed a leukocyte count of 6,200/µl, lymphocyte count of 924/µl, hemoglobin of 11.3 g/dl, ferritin of 4512 ng/ml, D-dimer of 3579 ng/dl, CRP of 6.3 mg/dl, LDH of 632 IU/l, interleukin-6 (IL-6) of 5.8 pg/ml, and creatinine of 1.3 mg/dl. Other laboratory results regarding electrolytes, liver enzymes, coagulation tests, and arterial blood gas analysis were normal. Due to suspicion of CNS infection, cerebrospinal fluid (CSF) was collected by lumbar puncture. Both nasopharyngeal and CSF samples were collected for real-time polymerase chain reaction (RT-PCR). No bacteria were observed on Gram staining of CSF sample.

Due to decreased $SatO_2$ and the onset of dyspnea during hospitalization, supplemental oxygen therapy with face mask was initiated. Intravenous fluids and 250 mg of intravenous methylprednisolone once a day were started. Methylprednisolone was gradually tapered based on patient's condition. Remdesivir 200 mg IV on the first day, then 100 mg once a day was started and continued for ten days. Enoxaparin 40 mg subcutaneously twice a day and famotidine 40 mg twice a day were administered. Further, interferon beta-1alpha 44 mcg subcutaneously was administered every 48 hours up to five doses. In addition, acyclovir 700 mg IV every eight hours was started with suspicion of herpes simplex virus (HSV) encephalitis.

On 6 December 2020, the results of SARS-CoV-2 RNA RT-PCR from CSF and nasopharyngeal samples were positive. CSF RT-PCR results for human immunodeficiency virus, HSV 1 and 2, cytomegalovirus, varicella-zoster virus, and Treponema pallidum were negative. It was concluded here that the patient had encephalitis associated with SARS-CoV-2. Hence, acyclovir was discontinued. During this course, the patient's status deteriorated and the $SatO_2$ tended to decrease further. The patient was intubated and transferred to the intensive care unit (ICU) on 8 December. Mannitol infusion was started. Based on IL-6 level of 125 pg/ml, tocilizumab 400 mg IV once daily was started and continued for two days. Dexamethasone 10 mg IV twice a day was also started. On the 16^{th} day of ICU admission, the patient's $SatO_2$ reached 96%. The laboratory markers were unremarkable and the patient was extubated. The patient's level of consciousness improved during this course. Oxygen supplement continued by non-rebreather mask. On 30 December 2020, the patient was discharged with good clinical conditions. However, mild headaches and slight dizziness remained for the patient for several days.

DISCUSSION

Although SARS-CoV-2 usually affects the respiratory system, it can invade other organs and cause complications, including myocardial infarction, kidney injury, hepatic impairment, thromboembolic events, and encephalitis. These manifestations can be due to direct virus invasion or para/post-infectious immune-mediated complications (10, 11). Patients with neurological involvement can present with headaches, dizziness, malaise, disorientation, stroke, and visual or motor impairment. However, some of these neurologic manifestations may be due to asymptomatic hypoxemia or hypoxemia related to acute respiratory distress syndrome (ARDS) (12, 13).

Our patient presented with mild hypoxemia without any respiratory distress. Also, supplemental oxygen did not initially change the patient's condition. Based on highly elevated D-dimer, ischemic changes in the brain were suspected, but no abnormality was observed in the brain CT scan. Also, the MRI showed no abnormality regarding lesions or encephalitis. Ye et al. reported a patient with encephalitis due to SARS-CoV-2 infection. The patient's brain CT scan was normal. Also, the results of CSF specimen PCR were negative, and anti-SARS-CoV-2 IgG/IgM was not detectable in these samples (14). Like our patient, imaging did not help in the diagnosis, but CSF PCR was positive for SARS-CoV-2.

To date, there is no definitive treatment for COVID-19 and its complications. In case of neurological involvement, supportive treatment is based on the prevention of seizures and worsening of lesions. Combination therapy with antiviral medications, interferon beta, intravenous immunoglobulins, and tocilizumab can be useful in treating COVID-19 encephalitis (15, 16). Furthermore, CSF collection, along with brain imaging, can help with diagnosis in these cases (15). SARS-CoV-2 PCR of CSF and nasopharyngeal samples were positive in our patient. However, no changes were observed in our patient's imaging regarding encephalitis. We successfully treated the patient with a combination of antiviral agents, corticosteroids, interferon beta, and tocilizumab. In the era of COVID-19 pandemic, encephalitis due to SARS-CoV-2 infection should be considered in a neurologically

symptomatic patient with a recent history of respiratory infections.

Conflict of interest

The authors declare that they have no conflicts of interests.

Consent

Written informed consent was not available because of change of residence but oral agreement from the patient was obtained.

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