CASE REPORT

Coronavirus Disease 2019 Complicated by Multiple Simultaneous Intracerebral Hemorrhages

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Abstract:
The relationship between coronavirus disease 2019 (COVID-19) and intracerebral hemorrhage remains unclear. We herein report a case of severe COVID-19 pneumonia complicated by multiple simultaneous intracerebral hemorrhages (MSICH). The patient died eight days after the episode of MSICH. No apparent coagulopathy was observed; however, extracorporeal membrane oxygenation and anticoagulation might have caused the occurrence of MSICH. Laboratory findings showed hypercoagulability, suggesting that thrombotic etiologies, such as sinus thrombosis or cerebral infarction, might also have caused MSICH. MSICH can occur as a fatal complication of COVID-19, and this should be considered when providing treatment.

Key words: COVID-19, SARS-CoV-2, intracerebral hemorrhage, ECMO, hypercoagulability, anticoagulant

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has become a global pandemic. COVID-19 can cause various thrombotic diseases, including cerebral infarction (1, 2). However, there are still a relatively limited number of reports describing intracerebral hemorrhage in COVID-19 patients (2-5), and the relationship between COVID-19 and intracerebral hemorrhage remains unclear.

We herein report a case of COVID-19 complicated by fatal multiple simultaneous intracerebral hemorrhages (MSICH).

Case Report

A Japanese man in his 50s, who was a non-smoker and had no medical history besides gout, developed a fever with cough and arthralgia. He had no history of going abroad and no obvious contact with a patient with COVID-19. His symptoms continued and he visited a hospital two days later. A chest radiograph showed signs of pneumonia, for which he was prescribed garenoxacin. Three days later, he developed shortness of breath and was subsequently diagnosed with COVID-19 based on the results of a reverse transcription polymerase chain reaction test for SARS-CoV-2. His respiratory dysfunction worsened rapidly. He was transferred to our hospital and underwent mechanical ventilation with deep sedation (-5 on the Richmond Agitation-Sedation Scale (6)).

Five days later, his pneumonia further deteriorated (Fig. 1), necessitating the introduction of extracorporeal membrane oxygenation (ECMO). He retained brainstem reflexes, including light reflex and cough reflex. The evaluation of other neurological findings was difficult because of deep sedation. Laboratory findings indicated increased levels of D-dimer and fibrinogen and a decreased platelet count. The prothrombin time (PT) and activated partial thromboplastin time (APTT) were not prolonged (Table).

Unfractionated heparin (5,000 units) was administered in-
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Figure 1. Chest radiographs one day (left) and five days (right) after hospital transfer showing the exacerbation of bilateral pulmonary opacification.

Figure 2. Cranial computed tomography images obtained six days after hospital transfer showing multiple hemorrhages in the bilateral cerebral hemispheres. There was a small hematoma in the midbrain. Arrows indicates fluid-blood levels in hematomas.

Table. Laboratory Findings after Hospital Transfer Showing Increasing Level of D-dimer without Prolongation of PT and APTT.

| Variables | Normal range (unit) | Days after the transfer |
|-----------|---------------------|------------------------|
| D-dimer   | 0-0.72 (μg/mL)      | 1.6 1.7 2.1 3.3 N/A    |
| PT        | 10.5-14.5 (sec)     | 14.7 14.2 13.8 14.2 N/A|
| APTT      | 27-37 (sec)         | 35.2 29.4 25.5 25.8 N/A|
| fibrinogen| 200-400 (mg/dL)     | 676.0 505.6 451.2 505.6 N/A|
| platelet  | 10-35 (10^4/μL)     | 20.0 16.4 12.2 8.2 6.6 |
| AST       | 8-38 (IU/L)         | 60 49 56 52 258        |
| ALT       | 4-44 (IU/L)         | 38 34 50 46 89         |
| T-Bil     | 0.22-1.2 (mg/dL)    | 1.36 0.93 0.92 1.17 6.76|
| CRE       | 0.6-1.1 (mg/dL)     | 0.95 0.79 0.72 0.70 11.71|
| BUN       | 8-20 (mg/dL)        | 13.6 10.8 13.2 14.3 197.5|

PT: prothrombin time, APTT: activated partial thromboplastin time, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, CRE: creatinine, BUN: blood urea nitrogen, N/A: not available

travenously to prevent thromboembolic complications with ECMO. His systolic blood pressure was controlled at 100-120 mmHg. Three hours after the introduction of ECMO, the patient suddenly developed a left dilated pupil and later developed bilateral fixed dilated pupils. The other brainstem reflexes also disappeared. Cranial computed tomography (CT) obtained the next day revealed severe MSICH in the bilateral cerebral hemispheres and the midbrain (Fig. 2), following which intensive treatments were withdrawn. Laboratory findings 13 days after the transfer showed severe renal
and liver dysfunction (Table), and the patient died the same day.

Discussion

MSICH accounts for 3.6%-5.9% of intracerebral hemorrhages, but it has rarely been reported as a complication of COVID-19. There is one report of MSICH that occurred with COVID-19, in which head CT showed multiple hematomas in the bilateral hemispheres, as in the present case (5). Coagulopathy was proposed as a possible cause of MSICH in that report because the hematomas were accompanied by findings of fluid-blood levels, which has a high specificity for patients with coagulopathy (7). In the present case, such a finding of fluid-blood levels was observed on CT images. However, the blood tests prior to the occurrence of MSICH showed no obvious coagulopathy because the PT and APTT were not prolonged. The laboratory findings did not meet the criteria for overt disseminated intravascular coagulation based on the International Society on Thrombosis and Hemostasis score (8).

Intracranial bleeding, including intracerebral hemorrhage, occurs in 2.4%-3.8% of patients receiving ECMO therapy (9, 10). There is a case report of a patient with MSICH following ECMO in which multiple subcortical hemorrhages were observed in the bilateral hemispheres (11). The mechanism underlying the development of bleeding following ECMO is not fully understood; however, the changes in hemodynamics or metabolism and the induction of coagulopathy are possible culprits. In addition, anticoagulation, which is required to avoid thrombus formation in the circuit, can also cause bleeding complications (11). Undetected coagulopathy induced by ECMO and heparin administration might have been related to the occurrence of MSICH in the present case. However, ECMO is essential for the treatment of severe pneumonia in COVID-19, and anticoagulant therapy is inevitable to treat thrombotic complications in COVID-19. These dilemmas regarding ECMO and anticoagulants show extreme difficulty in the management of COVID-19. The relationships between ECMO or heparin administration and MSICH remain unclear in the present case. However, these bleeding risks should be considered when using ECMO and anticoagulants in the treatment of COVID-19.

In conclusion, MSICH can occur as a fatal complication of COVID-19. There is a report of a COVID-19 patient suspected of having cerebral vasculitis, in which brain magnetic resonance imaging revealed ischemia and hemorrhage in the territories of perforating arteries (20). Vasculitis can cause the disruption of vessels and subsequent bleeding, so cerebral vasculitis induced by SARS-CoV-2 may be another possible cause of MSICH in the present case.

SARS-CoV-2 may spread from the respiratory tract to the brain via the olfactory nerve or circulatory systems, which can cause intracranial infections following pneumonia (18). Intracranial infections, such as meningoencephalitis, can also cause intracerebral hemorrhage in COVID-19 (4). Intracranial infections were not explored in the present case; however, such invasion from the lung to the brain might have existed because MSICH occurred as the second event following pneumonia.

Cerebral herniation due to MSICH was considered as the cause of death based on the neurological findings; however, follow-up CT was not performed to confirm this because of clinical deterioration. The laboratory findings on the last day demonstrated on imaging studies due to the rapid clinical deterioration in the present case; however, the blood tests before the occurrence of MSICH revealed elevated levels of D-dimer and fibrinogen, which indicated that the patient was in a hypercoagulable state. Regarding the observed hypercoagulability, thrombosis in the dural sinuses and cortical veins, or multiple cerebral infarctions with hemorrhagic transformation may be other candidates responsible for MSICH in the present case.

There is a report of cases with COVID-19 complicated with cerebral infarction and antiphospholipid antibodies, which are autoantibodies that increase the risk of thrombotic diseases and can arise transiently in patients with critical illness and various infections (1). Antiphospholipid antibodies were not evaluated in the present case, but they may have caused the occurrence of MSICH.

The authors state that they have no Conflict of Interest (COI).

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