

Characteristics of Coagulation/Fibrinolysis Abnormalities in Serious Corona Virus Disease 2019 (COVID-19) Patients Complicated with Stroke: Case Series

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Case report

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Abstract

Background: Not surprisingly, novel coronavirus disease 2019 (COVID-19) patients are frequently complicated with COVID-19 associated coagulopathy (CAC). And cerebrovascular disease is not uncommon during SARS-CoV-2 infection, especially in older patients and severe patients with risk factors. This time we treated six patients with serious COVID-19, of whom two had a stroke during ICU admission. Based on our experience, we report some findings on the relationship between CAC pattern and risk of stroke in patients with serious COVID-19.

Case presentation: Two patients who subsequently had a stroke were transferred to our emergency center and underwent veno-venous extracorporeal corporeal membrane oxygenation (V-V ECMO) with unfractionated heparin as an anticoagulant for treatment of severe respiratory failure. In one patient, the platelet count was $5.7 \times 10^4/\text{mm}^3$ on ICU admission, increased to above $10 \times 10^4/\text{mm}^3$ after 5 days. In the other patient, the platelet count progressed to above $10 \times 10^4/\text{mm}^3$ for the observation period of 8 days. Both prothrombin-international normalized ratio and activated partial thromboplastin time remained almost within the normal ranges throughout the 8-day period. In contrast, the levels of fibrin degradation products, D-dimer, and plasmin alfa2-plasmin inhibitor complex remained above the upper limits of the normal ranges throughout the 8-day period, and the levels in both cases increased markedly around the onset of stroke.

Discussion: From these findings, we gained a strong impression that the pattern of CAC in stroke patients was not a “suppressed-fibrinolytic type” pattern, but rather an “enhanced-fibrinolytic type” pattern.

Conclusions: During the period in which serious COVID-19 patients undergo V-V ECMO, we need to be aware that these patients with CAC may be complicated with stroke not only cerebral infarction, but also cerebral hemorrhage.

Background

Not surprisingly, serious novel coronavirus disease 2019 (COVID-19) patients are frequently complicated with coagulation/fibrinolysis abnormalities which called COVID-19 associated coagulopathy (CAC) because the disease arises from infection with severe acute respiratory syndrome coronavirus (SARS-CoV)-2.

Typically, the coagulation/fibrinolysis abnormalities caused by infection are “suppressed-fibrinolysis type” abnormalities¹⁾. Activation of the host defense systems against infection results in coagulation activation and thrombin generation as critical communication components among the humoral and cellular amplification pathways, a condition known as thromboinflammation or immunothrombosis²⁾.

Thus far, we have treated six patients with serious COVID-19 and investigated the transition of their coagulation/fibrinolysis condition. Five of the patients were treated with veno-venous extracorporeal corporeal membrane oxygenation (V-V ECMO), of whom two patients had a stroke. Based on the

treatment of these patients, we strongly suspected that the CAC at the time of progression to serious condition was not “suppressed-fibrinolytic type” abnormalities but rather “enhanced-fibrinolytic type” abnormalities, despite COVID-19 being an infectious disease.

To date, there have been few reports discussing the relationship between coagulation/fibrinolysis abnormalities and risk of stroke, focusing on patients with serious COVID-19. We report two cases of serious COVID-19 complicated with stroke during V-V ECMO and propose that it is particularly important to identify the situation of CAC quickly for prevention of stroke complications.

Before publishing our case series at the present time, and considering the disease-specificity of COVID-19, we obtained approval from the Fukuoka University Medical Ethics Committee (approval number: U20-07-001). And we also obtained written and signed consent to publish information from all patients or their proxies.

Case Presentation

Patient characteristics

We treated six serious COVID-19 patients in our ICU between 10 April 2020 and 15 June 2020. The characteristics of these patients are shown in Table 1. Serious status was defined as cases who were managed with mechanical ventilation (MV) and/or V-V ECMO because their PaO₂/FiO₂ ratio was <200.

Five of the patients were men, and all six patients were diagnosed with COVID-19 by detection of SARS-CoV-2 RNA in nasopharyngeal swab specimens by a polymerase chain reaction test. The patients entered a critical state caused by hypo-oxygenation and were transferred from their previous hospital to our ICU under endotracheal intubation with MV. The PaO₂/FiO₂ ratio at ICU admission was 116 in Case 3, as the only patient whose PaO₂/FiO₂ ratio exceeded 100, and less than 100 in the other five cases, indicating that oxygenation was extremely poor. Consequently, V-V ECMO was introduced in all cases, except for Case 2 who did not meet the ECMO inclusion criteria because he was aged above 65 years and had been under MV management at a previous hospital for more than 1 week. Medical history was found in all patients, except for Case 5. Their Acute Physiology And Chronic Health Evaluation (APACHE) II scores³ on admission to our ICU were 21 to 28, and their Sequential Organ Failure Assessment (SOFA) scores⁴ were 7 to 14. From these scores, the predicted mortality rate of the six cases was ≥50%.

Case 1 had multiple hemorrhagic cerebral infarctions on hospital day 6, and Case 3 had cerebral hemorrhage at the subcortical right cingulate gyrus and left middle frontal gyrus on hospital day 6 (Figure 1). The infarctions in Case 1 were triggered by withdrawal from the treatment that had been given until then, including continuous administration of unfractionated heparin (UFH) as an anticoagulant for V-V ECMO, and the patient died on hospital day 12. Case 3 continued the treatment that had been given up to then, and withdrew from V-V ECMO on hospital day 14. Although he subsequently developed symptomatic epilepsy, the control by oral medication was good, and there were no other neurological sequelae. He was transferred to the previous rural hospital on hospital day 56. In addition to Case 1, Case

2, for whom V-V ECMO was not performed, died on hospital day 8. Overall, V-V ECMO was performed in five cases, of whom one died (Case 1), three withdrew from MV and V-V ECMO, and one (Case 5) was managed by MV and V-V ECMO for more than 2 months.

Blood coagulation/fibrinolysis markers and DIC diagnostic criteria scores at ICU admission

▣ Blood coagulation/fibrinolysis markers

Table 2 shows the blood coagulation/fibrinolysis markers at the time of ICU admission.

1) All COVID-19 patients

Among all six cases, five cases other than Case 3 had platelet count of $10 \times 10^4/\text{mm}^3$ or more, and five cases other than Case 6 had prothrombin time-international standard ratio (PT-INR), activated partial thromboplastin time (APTT), and antithrombin (AT) activity within the normal ranges. Meanwhile, thrombin-antithrombin complex (TAT) exceeded the upper limit of normal in all cases. On the contrary, fibrin/fibrinogen degradation product (FDP) and D-dimer exceeded the upper limit of normal in all cases and plasmin alfa2-plasmin inhibitor complex (PIC) was above the upper limit of normal range in five cases. Plasminogen activator inhibitor (PAI)-1 was elevated above the upper normal limit in Cases 1 and 6, but was within the normal limits in the other cases. Fibrinogen (Fbg) was above the upper limit of normal range in five cases.

2) Two COVID-19 patients complicated with stroke

In the two stroke cases, platelet count at ICU admission was $5.7 \times 10^4/\text{mm}^3$ in one patient and $\geq 10 \times 10^4/\text{mm}^3$ in the other patient. In both patients, PT-INR and APTT were within the normal ranges, while TAT was above the upper limit of normal. In contrast, FDP/D-dimer and PIC remained above the upper limits of the normal ranges. PAI-1 was elevated in Case 1, but was in the normal range in Case 3.

▣ Disseminated intravascular coagulation (DIC) diagnostic criteria scores

Table 2 shows the various DIC diagnostic criteria scores upon ICU admission.

1) All COVID-19 patients

When the DIC scores were calculated using the major DIC diagnostic criteria, four of the six cases were diagnosed as DIC by the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria⁵⁾, none of the six cases were diagnosed as DIC by the International Society on Thrombosis and Hemostasis (ISTH) overt DIC diagnostic criteria⁶⁾, and two of the six cases were diagnosed as DIC by the Japanese Society on Thrombosis and Hemostasis (JSTH) DIC diagnostic criteria (infectious type)⁷⁾. These results indicate that whether or not a serious COVID-19 patient was diagnosed with DIC depended on the DIC diagnostic criteria used.

2) Two COVID-19 patients complicated with stroke

Neither of the two cases with stroke were diagnosed as DIC by the ISTH overt DIC diagnostic criteria. However, Case 3 was diagnosed as DIC according to the JAAM and JSTH (infectious type) DIC diagnostic criteria.

▣ Time courses of global blood coagulation/fibrinolysis markers

The daily changes in coagulation/fibrinolysis markers up to hospital day 8 are shown in Figure 2 (global blood coagulation/fibrinolysis markers) and Figure 3 (blood coagulation/fibrinolysis markers).

1) All COVID-19 patients

Platelet count did not decrease sharply and remained above $10 \times 10^4/\text{mm}^3$ throughout the observation period, except in Case 3. PT-INR for all patients remained within the 0.9-1.2 range during the follow-up period and did not deviate significantly from the normal range. APTT exceeded the normal upper limit in all cases other than Case 3 during the observation period, but did not extend much beyond than 45 s in all cases except Case 6. Fbg remained above the upper limit of normal range in four cases during the observation period, and never decreased below the lower limit of normal in all cases during the observation period. Although varying degrees were observed depending on individual cases, FDP/D-dimer exceeded the normal upper limit in all cases during the observation period. In Cases 1 and 3, these markers decreased once in the middle of the observation period, but sharply increased again from day 6. Furthermore, in Case 2, these markers rose again from day 8. Despite varying degrees in different cases, TAT exceeded the normal upper limit in all cases except Case 4 during the observation period. This marker decreased once in the middle of the observation period, but sharply rose again from day 6 in Cases 1, 3, and 5. PIC also exceeded the normal upper limit in all cases except Case 4 during the observation period, although there were differences in degree depending on the individual cases. This marker decreased once in the middle of the observation period, but sharply increased again from day 7 in Cases 1 and 3. In some cases, PAI-1 increased above the normal upper limit of 50 ng/mL, and increased above 100 ng/mL in only two cases (Cases 1 and 6). AT activity in two cases (Cases 2 and 6) decreased to <50% during the observation period, and only one case (Case 6) received administration of recombinant human AT (rhAT; antithrombin gamma) at 1,800 U/day from day 2 for a period of 5 days.

2) Two COVID-19 patients complicated with stroke

Cases 1 and 3 developed stroke on day 6. Both cases were confirmed to have re-elevation of FDP/D-dimer and PIC at the same time as the onset of stroke, with TAT increasing at 1 day before these markers were re-elevated. There were no significant changes in PT-INR, APTT, and PAI-1 in both cases at that time. In Case 3, the platelet count decreased on day 6 and Fbg decreased on day 7. In Case 1, the platelet count did not change at that time and Fbg decreased on day 8.

▣ Time courses of DIC diagnostic criteria scores

The daily changes in the various DIC diagnostic criteria scores up to hospital day 8 are shown in Figure 4.

Four cases (Cases 2, 3, 5, and 6) were diagnosed with DIC based on the JAAM DIC criteria on admission to the ICU. In these cases, recombinant human soluble thrombomodulin (rhsTM; thrombomodulin alfa) at 380 U/kg/day was administered from day 1 (Figure 4). In three of the four cases (Cases 2, 5, and 6), DIC was resolved at the end of rhsTM treatment. Although Case 1 had a score of 5 on day 6 and was diagnosed with DIC, rhsTM was not administered because multiple hemorrhagic cerebral infarctions were present on the same day. In addition, because the AT activity in Case 6 was 42% on the second day, this case started additional supplementation with rhAT at 1,800 U/day for 5 days from the same day (Figure 4). Using the ISTH overt DIC criteria, only Case 3 was diagnosed with DIC on hospital day 8. According to the JSTH DIC criteria (infectious type), two cases (Cases 2 and 3) diagnosed with DIC on ICU admission subsequently recovered from DIC. However, DIC recurred in Case 3, and eventually two patients (Cases 1 and 3) were diagnosed as DIC on hospital day 8.

Discussion

COVID-19 is well-known to be frequently associated with coagulation/fibrinolysis abnormalities⁸⁻¹⁰). Thus far, we have managed six serious COVID-19 patients, and all of whom had already developed CAC at the time of ICU admission without exception.

Recently, DIC (i.e., coagulation/fibrinolysis abnormalities) has been classified into three types depending on the pattern of the fibrinolytic system¹¹⁻¹²). All three types involve significant activation of coagulation. The first pattern is “suppressed-fibrinolytic-type” abnormalities. This pattern is characterized by severe coagulation activation but mild fibrinolytic activation, and is typically seen in sepsis. Because there is a marked increase in the fibrinolytic inhibitory factor PAI-1, an important factor for DIC characterization, fibrinolysis is strongly suppressed. The second pattern is “enhanced-fibrinolytic-type” abnormalities. This pattern is characterized by marked fibrinolysis activation that corresponds to coagulation activation, and is typically seen in acute promyelocytic leukemia (APL), abdominal aortic aneurysm, and prostate cancer. Fibrinolysis is strongly activated, with hardly any elevation of PAI, and hemostatic plugs (thrombi due to hemostasis) are quite easily dissolved. Laboratory findings show marked elevations in both TAT and PIC, as well as elevations in FDP and D-dimer. The third pattern is “balanced-fibrinolytic-type” abnormalities. This pattern is characterized by a balance between the coagulation and fibrinolytic activations and is thus an intermediate pathology between the other two types of DIC described above.

In “fibrinolysis-suppressed type” abnormalities derived from infectious diseases, microthrombi formed in peripheral blood vessels due to hypercoagulability are difficult to dissolve, and systemic microcirculatory disorders occur, resulting in complications such as organ failure, cerebral infarction, and myocardial infarction. However, bleeding symptoms are relatively mild. Meanwhile, in “fibrinolysis-enhanced type” abnormalities, almost no increase in PAI is observed, and thus the microthrombi are easily dissolved and the risk of complications with bleeding symptoms such as cerebral hemorrhage, epistaxis, and subcutaneous hematoma increases. However, organ dysfunction seldom occurs.

Because our six cases were all serious COVID-19 patients, we expected that they would have “fibrinolysis-suppressed type” coagulation/fibrinolysis abnormalities. However, in all cases except Case 6 at ICU admission, the coagulation markers PT-INR and APTT were within the normal ranges, and APTT was prolonged within the set range because of UFH use as an anticoagulant for ECMO. Meanwhile, PT-INR and APTT did not deviate from the normal values any more than expected. PAI-1 on ICU admission was within the normal range except for two cases (Cases 1 and 6) and no significant increases were observed thereafter except in Case 6. However, both TAT and PIC were significantly increased on admission to the ICU. The levels of these markers then decreased once, but increased again on hospital day 6 or 7. Similarly, FDP and D-dimer were significantly increased on admission to the ICU, then decreased once and subsequently increased again on hospital day 7. From these results, we strongly suspected that serious COVID-19 patients had sufficiently enhanced fibrinolysis as well as coagulation at the time of ICU admission, and that despite COVID-19 being an infectious disease, the pattern of CAC was of the “enhanced-fibrinolysis type” rather than the “suppressed-fibrinolysis type”.

Levi et al.⁸) commented that coronavirus infections are associated with surprising activation of the fibrinolytic system and that this can be explained by elevated FDP/D-dimer due to massive release of plasminogen activators in response to inflammation-induced endothelial cell damage in patients with severe COVID-19. In addition, Iba et al.¹³) suspected that secondary hyperfibrinolysis following coagulation activation plays a dominant role in the CAC, based on the results of an observational study, in which the maximum score among the DIC parameters in non-survivors was the D-dimer level¹⁴). In particular, two cases (Cases 1 and 3) were complicated with stroke on hospital day 6 and we confirmed that FDP/D-dimer and PIC were re-elevated at the same time as the stroke onset. In addition, TAT was re-elevated at 1 day before these markers became re-elevated. However, we also confirmed that the coagulation markers PT-INR and APTT were within the normal ranges and that Fbg was not decreased, reflecting inflammation. In other words, these two cases that developed stroke appeared to shift their pattern of coagulation/fibrinolysis abnormalities to the “enhanced-fibrinolysis type” before and after the onset of stroke. For this reason, we suspect that serious COVID-19 patients need to be observed carefully for not only thrombus formation due to hypercoagulability, but also hemorrhagic complications due to hyperfibrinolysis.

In a review article, Connors et al.¹⁵) described that, unlike other RNA-type viruses associated with hemorrhagic manifestations such as Ebola and hemorrhagic fever viruses, the coagulopathy seen with SARS-CoV-2 has not been reported to result in significant bleeding. We experienced stroke complications in two of our six cases with serious COVID-19. Therefore, we consider that the frequency of intracranial events is as not low as previously indicated, especially when the condition of COVID-19 patient progresses to the serious stage.

Several other hypotheses can be considered as the underlying mechanism of stroke in serious COVID-19 patients. First, including the cases we experienced in this series, serious COVID-19 patients exhibit multiple microthrombi formation in the peripheral vessels because elevated FDP/D-dimer is often observed, and are considered to be at high risk of cerebral infarction. Second, some severely ill patients

with SARS-CoV-2 infection may have severe thrombocytopenia, a high-risk factor for cerebral hemorrhage. In addition, we believe that increased fibrinolysis associated with multiple microthrombi may be a risk factor for hemorrhagic cerebral infarction.

We speculate that neurologic injury will be another mechanism leading to stroke in patients with COVID-19. Researchers have reported the detection of SARS-CoV nucleic acids in cerebrospinal fluid samples from patients infected with respiratory viruses such as SARS and Middle East respiratory syndrome (MERS) as well as in their brain tissues such as glial cells and neurons on autopsy, which makes them a potential target for COVID-19 (16-18). SARS-CoV-2 belongs to the same large family of coronaviruses as SARS-CoV and MERS-CoV, and may thus be able to enter the central nervous system via the hematogenous or retrograde neural pathways. The latter is supported by findings that SARS-CoV can lead to neuronal death in mice by invading the brain through the nose close to the olfactory epithelium (18) and that some patients with COVID-19 have smell impairment (19).

Similar to SARS-CoV, SARS-CoV-2 has been shown to interact with host angiotensin-converting enzyme (ACE) 2 receptor to invade inside cells. It was also demonstrated that the ACE2-binding affinity of the SARS-CoV-2 spike protein was 10–20 fold higher than that of the SARS-CoV spike protein (20). After SARS-CoV-2 invades nerve cells and vascular endothelial cells, it damages these tissues, leading to fluctuations in vasoconstriction. For these reasons, there may be an increased risk of cerebrovascular disease in serious COVID-19 patients.

The following mechanism is considered a secondary factor. Serious COVID-19 patients frequently undergo V-V ECMO to avoid continuous hypoxemia. In our series, V-V ECMO was performed in all cases, except for Case 2 who was contraindicated for this intervention. Usually, a relatively high dose of anticoagulant is administered to prevent thrombus formation during V-V ECMO. Together with this factor, one of the main adverse events during ECMO is hemorrhage complications. During ECMO performance in a previous study, $\geq 50\%$ of patients had bleeding complications and 3.8% experienced intracranial hemorrhage (21). When we re-examined our serious COVID-19 patients who underwent V-V ECMO, UFH was used as an anticoagulant in the early stages of their management in the ICU. Cases 1, 3, and 4 fell into this category. In Cases 5 and 6, the anticoagulant was changed to nafamostat mesylate to avoid hemorrhagic complications as much as possible. As a result, no hemorrhagic complications were observed. Therefore, we conclude that use of UFH as an anticoagulant for V-V ECMO may have indirectly contributed to intracranial hemorrhage. When serious COVID-19 patients are administered UFH as an anticoagulant for V-V ECMO, the dose should be reduced below the usual dose and APTT, which is normally controlled at 60–80 s for monitoring the UFH dose, should be controlled at 40–60 s (or usually less than twice the upper limit) (22)–(24). To determine the dose of UFH more precisely, use of thromboelastography (TEG), such as TEG® or ROTEM® (rotational thromboelastometry), to accurately evaluate the blood coagulation fibrinolytic kinetics over time is one possible strategy. In addition, the dose of UFH should be adjusted frequently. Alternatively, the use of nafamostat mesylate, which has few hemorrhagic complications, as an anticoagulant may be considered. This is possible because nafamostat mesylate effectively blocks the early stages of SARS-CoV-2 infection by blocking the viral

entry process through inhibition of fusion between the virus outer membrane and the cell membrane of SARS-CoV-2-infected host cells²⁵).

In this series, four of six serious COVID-19 patients were diagnosed with DIC according to the JAAM DIC diagnostic criteria, and were administered rHsTM. In Japan, when attempting anticoagulant therapy for DIC, it is necessary to calculate DIC scores using DIC diagnostic criteria. In the most recent Japanese sepsis guidelines²⁶), use of the JAAM DIC diagnostic criteria is recommended for diagnosis of DIC in patients with infection, especially sepsis. Furthermore, rHsTM is the most frequently used anticoagulant for treatment of DIC in Japan. Meanwhile, the DIC pattern in serious COVID-19 patients is not “suppressed-fibrinolysis type” abnormalities, but rather “enhanced-fibrinolysis type” abnormalities, and this pattern is different from the usual DIC pattern of infectious diseases. Therefore, the necessity of DIC treatment is also debated.

We decided to administer rHsTM to serious COVID-19 patients with DIC for the reasons described below. Use of rHsTM as an anticoagulant is a promising treatment strategy to safely rescue patients with APL from life-threatening coagulopathy²⁷). APL is also a representative disease with the pattern of “enhanced-fibrinolysis type” coagulation/fibrinolysis abnormalities. Furthermore, resolution of DIC by rHsTM administration was reported to improve overall survival, regardless of disease severity, in patients with infectious diseases²⁸). The reason why we choose rHsTM as an anticoagulant was that it only exhibits anticoagulant effects under conditions of thrombin over-production²⁹), resulting in fewer adverse bleeding events. Furthermore, thrombin activatable fibrinolysis inhibitor, which is physiologically activated by the thrombin-thrombomodulin complex, down-regulates fibrinolysis and has the potential to regulate hyperfibrinolysis-induced hemorrhage³⁰). Patients were administered rHsTM at 380 U/kg/day for around 1 week with daily evaluation of the JAAM DIC score. DIC was resolved in three of the four cases within ICU day 4, and the other one case complicated with cerebral hemorrhage (Case 3) had a score decrease to 4 and improved coagulation/fibrinolysis abnormalities. Therefore, we consider that the anticoagulant rHsTM is well worth using for serious COVID-19 patients who undergo V-V ECMO. However, in Case 3, FDP/D-dimer and PIC increased from the day after the end of rHsTM administration and TAT increased from the end of administration, resulting in recurrent coagulation/fibrinolysis abnormalities. Therefore, we suggest that rHsTM administration should be prolonged to prevent stroke in serious COVID-19 patients.

There are some limitations to the present study. First, the case series comprised only six patients and the study had a retrospective observational design. Second, ECMO was performed in all patients except one from the day of ICU admission, and anticoagulants such as UFH and nafamostat mesylate were administered to prevent blood clots in the ECMO circuit.

Conclusions

The pattern of CAC was not “suppressed-fibrinolytic type” abnormalities but rather “enhanced-fibrinolytic type” abnormalities, despite COVID-19 being an infectious disease.

During the period in which COVID-19 patients became more serious and frequently underwent V-V ECMO, we need to be aware that these patients with coagulation/fibrinolysis abnormalities may be complicated with not only cerebral infarction, but also cerebral hemorrhage. When serious COVID-19 patients are administered UFH as an anticoagulant during V-V ECMO, the dose of UFH should be reduced below the usual dose and APTT should be controlled at 40–60 s (or usually less than twice the upper limit) to avoid hemorrhage.

List Of Abbreviations

ACE; angiotensin-converting enzyme

APACHE; Acute Physiology And Chronic Health Evaluation

APL; acute promyelocytic leukemia

APTT; activated partial thromboplastin time

AT; antithrombin

COVID-19; coronavirus disease 2019

DIC; disseminated intravascular coagulation

Fbg; fibrinogen

FDP; fibrin/fibrinogen degradation product

ISTH; International Society on Thrombosis and Hemostasis

JAAM; Japanese Association for Acute Medicine

JSTH; Japanese Society on Thrombosis and Hemostasis

MERS; Middle East respiratory syndrome

MV; mechanical ventilation

PAI; plasminogen activator inhibitor

PIC; plasmin alfa2-plasmin inhibitor complex

PT-INR; prothrombin time-international standard ratio

rhAT; recombinant human

rhsTM; recombinant human soluble thrombomodulin

SARS-CoV; severe acute respiratory syndrome coronavirus

SOFA; Sequential Organ Failure Assessment

TAT; thrombin-antithrombin complex

UFH; unfractionated heparin

V-V ECMO; veno-venous extracorporeal corporeal membrane oxygenation

Declarations

Ethics approval and consent to participate

Written informed consent in accordance with the Declaration of Helsinki and approved by the the Fukuoka University Medical Ethics Committee (approval number: U20-07-001) was obtained from all patients or their proxies for the publication of this Case report. We are always prepared to provide a copy of the informed consent document at the request of the editorial department.

Consent for publication

Before publishing our case series at the present time, and considering the disease-specificity of COVID-19, we obtained written and signed consent to publish information from all patients or their proxies.

We are always prepared to provide a copy of the informed consent document at the request of the editorial department.

Availability of data and materials

The almost all data generated or analyzed during this study are included in this published article. In addition, other datasets used and/or analyzed during the study are available from the corresponding authors upon reasonable request.

Competing Interests

HI reports speakers' bureau fees, consultancy, and research funding from ASAHI KASEI FARMA.

The other authors declare that there is no conflict of interest.

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Authors' contributions

HI contributed to the study design, analysis, interpretation of the results, drafting of the manuscript, and critical revisions of the manuscript for intellectual content. JM, YI, SM, KT, YI, and TK contributed to data acquisition, analysis and interpretation of data. MI contributed to the interpretation of brain and chest CT scan, and chest X-ray. KH was a contributor in data collection, assembly of data and writing the manuscript. YN analyzed and interpreted the patient data and performed analysis, and revisions of the manuscript.

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Authors' information

HI belongs to the Japan Society for Thrombosis and Hemostasis and a member of the DIC Section of Scientific Standardization Committee.

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

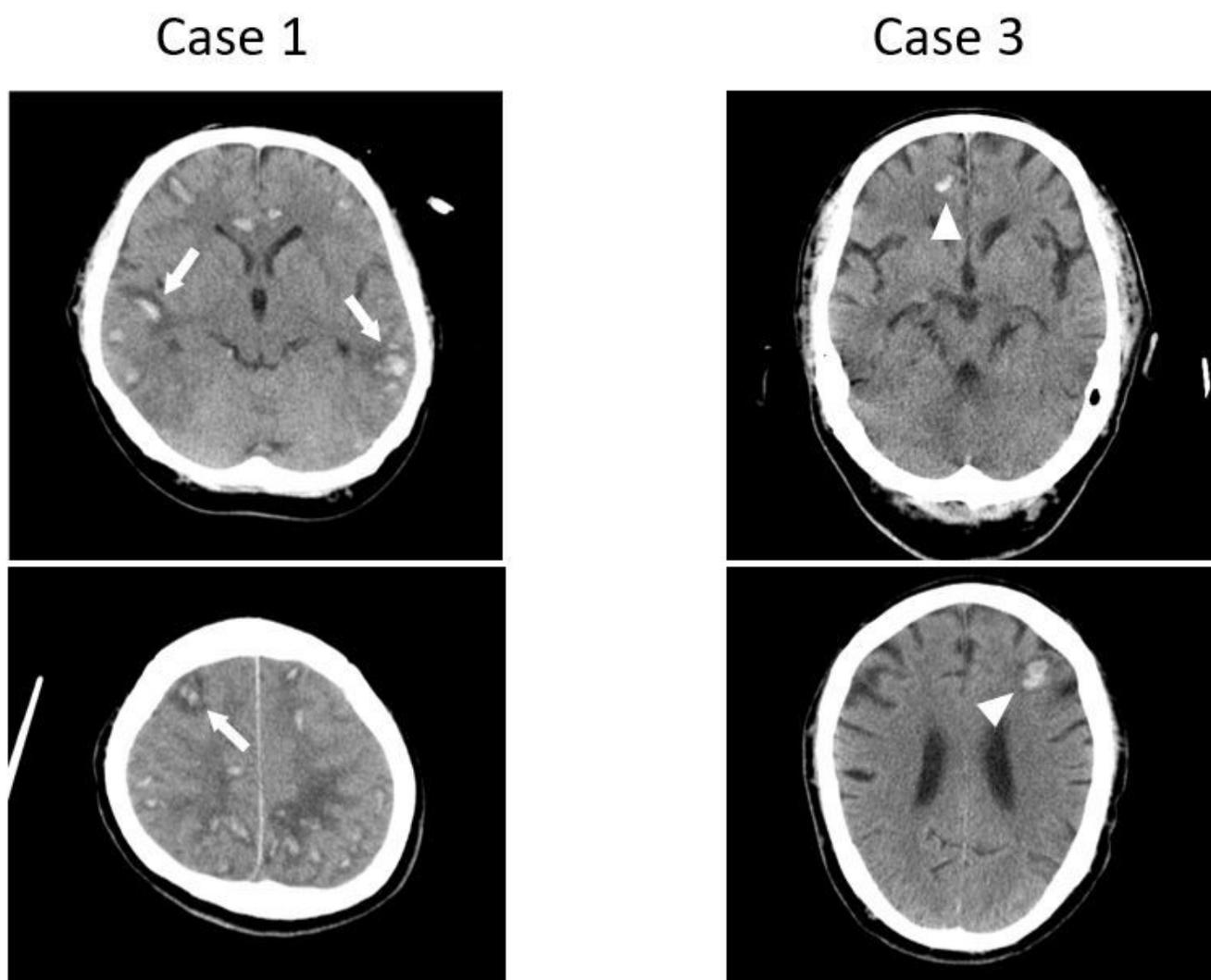


Figure 1

Brain computed tomography (CT) scans in Case 1 and Case 3. Left: Images of a brain CT scan in Case 1 at 6 days after ICU admission. The findings confirmed the presence of heterogeneous high-density areas at the subcortex of the right superior frontal gyrus, right superior temporal gyrus, and left middle temporal gyrus (white arrows). These high-density areas are surrounded by low-density areas, and the boundary between the areas is unclear. The findings also confirmed the presence of multiple slight high-density spots at the supratentorial subcortex surrounded by low-density areas, and the boundary between these areas is unclear. These findings are diagnosed as cerebral hemorrhagic infarction. Right: Images of a brain CT scan in Case 3 at 6 days after ICU admission. The findings confirmed the presence of two homogeneous high-density areas with irregular borders at the subcortical right cingulate gyrus and left middle frontal gyrus (white arrowheads). These high-density areas (white areas) are diagnosed as intracerebral subcortex hemorrhage. Reprinted from Japanese Journal of Thrombosis and Hemostasis. 2020;31(4):398-408. DOI: <https://doi.org/10.2491/jjsth.31.398>. Approved by the editor-in-chief.

Figure 2

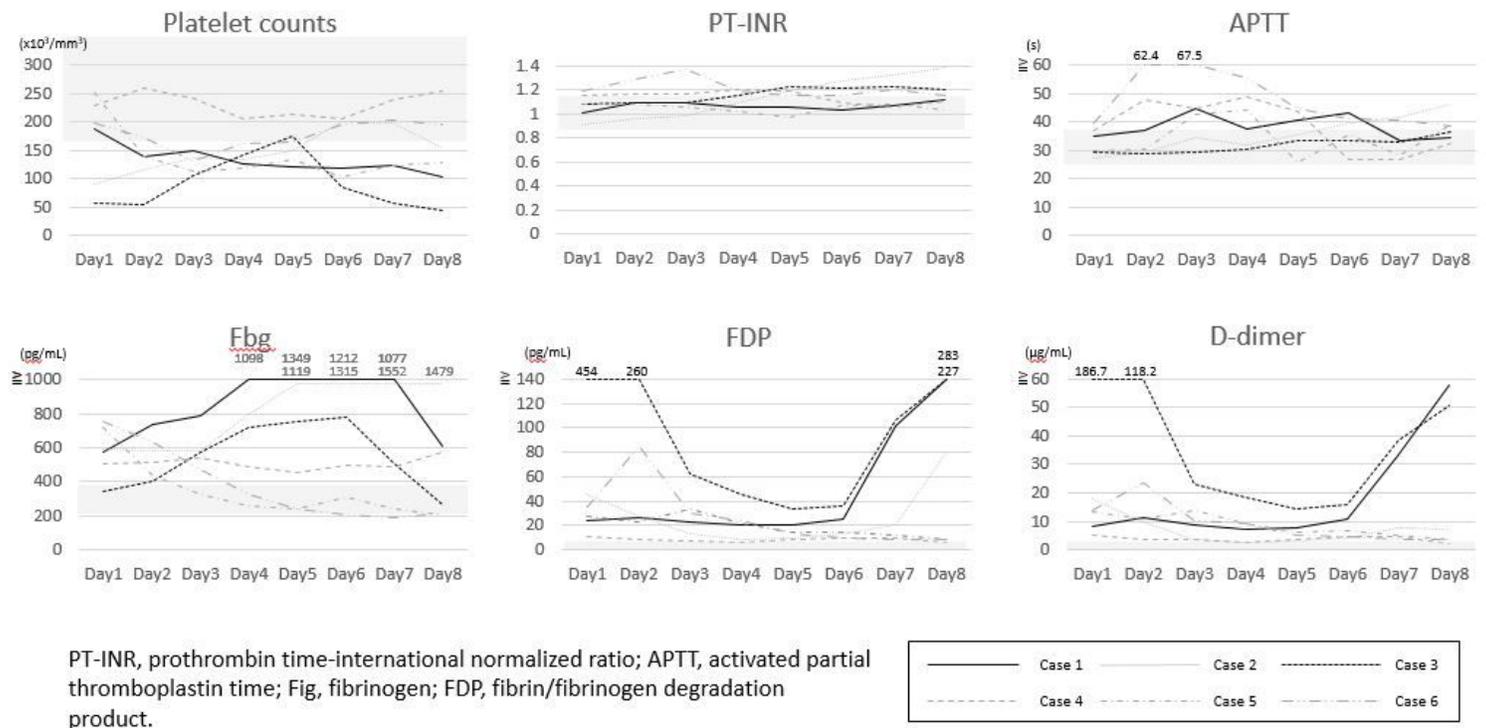
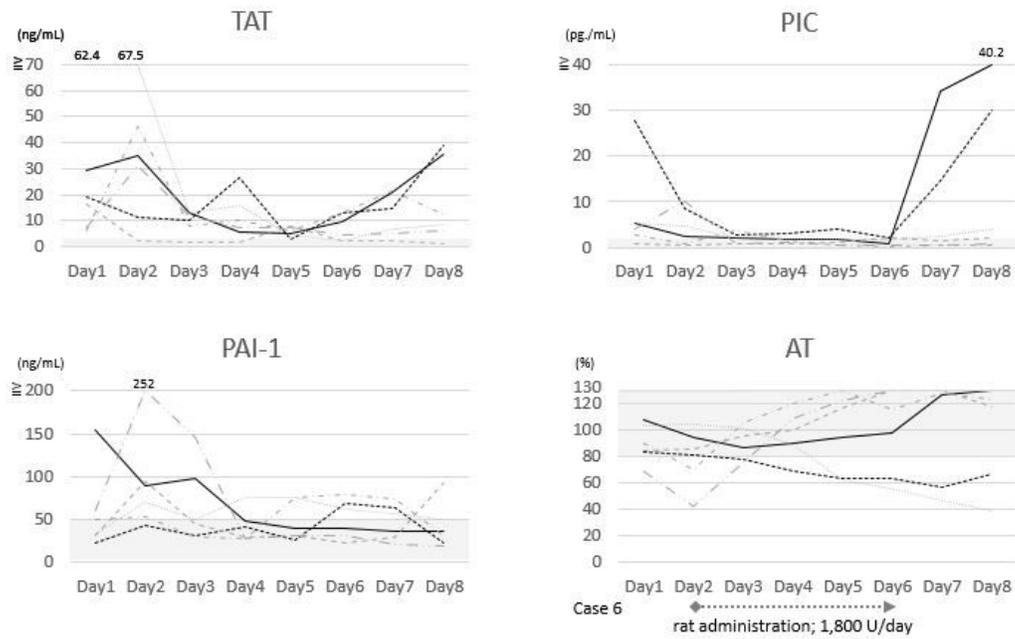


Figure 2

Dynamic profiles of global blood coagulation/fibrinolysis markers in severe COVID-19 patients. The solid black line (Case 1) and thin dashed black line (Case 3) indicate the patients with stroke. The gray bands indicate the normal ranges.

Figure 3



TAT, thrombin-antithrombin complex; PIC, plasmin alfa2-plasmin inhibitor complex; PAI-1, plasminogen activator inhibitor-1; AT, antithrombin.

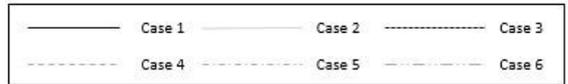
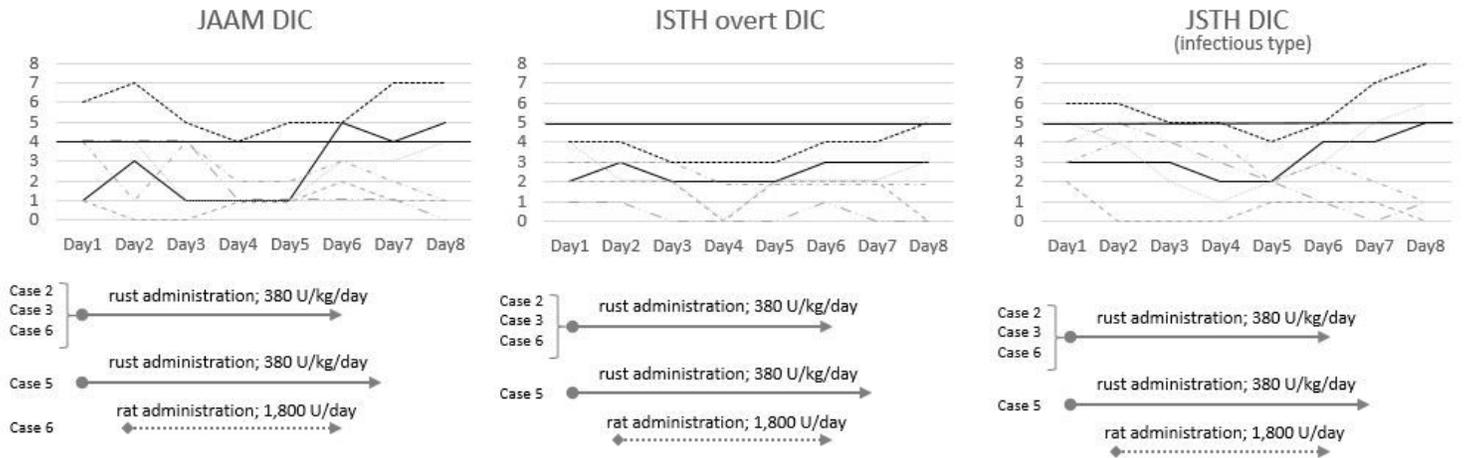


Figure 3

Dynamic profiles of blood coagulation/fibrinolysis markers in severe COVID-19 patients. The solid black line (Case 1) and thin dashed black line (Case 3) indicate the patients with stroke. The gray bands indicate the normal ranges. Reprinted from Japanese Journal of Thrombosis and Hemostasis. 2020;31(4):398-408. DOI: <https://doi.org/10.2491/jjsth.31.398>. Approved by the editor-in-chief.

Figure 4



DIC, disseminated intravascular coagulation; COVID, coronavirus; JAAM, Japanese Association for Acute Medicine; ISTH, International Society on Thrombosis and Hemostasis; JSTH, Japanese Society on Thrombosis and Hemostasis; rust, recombinant human soluble thrombomodulin; rat, recombinant human antithrombin.



Figure 4

Dynamic profiles of various DIC diagnostic criteria scores in severe COVID-19 patients. The solid black line (Case 1) and thin dashed black line (Case 3) indicate the patients with stroke. The horizontal thick black line indicates the score for diagnosing DIC according to each set of DIC diagnostic criteria. The JSTH DIC score in Case 6 is a reference value because rhAT was replenished for 5 days from day 2. Reprinted from Japanese Journal of Thrombosis and Hemostasis. 2020;31(4):398-408. DOI: <https://doi.org/10.2491/jjsth.31.398>. Approved by the editor-in-chief.

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