CASE REPORT

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Hemorrhagic transformation in SARS-CoV-2 infected patients: case reports from Indonesia

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ABSTRACT

Introduction: While initially suggested as a primary respiratory infection, there has been increasing proof that the novel coronavirus disease (COVID-19) also leads to severe neurological manifestation particularly ischemic stroke. The hypercoagulable state observed in COVID-19 patients is thought to contribute to this phenomenon although the exact pathophysiology is still unclear.

Case: We are reporting two cases of hemorrhagic transformation after ischemic stroke in COVID-19 patients. Both patients were women presenting with ischemic stroke and bronchopneumonia due to COVID-19. They both experienced prolonged coagulation studies before sudden neurological deterioration. Evaluation CT scan demonstrated the hemorrhagic transformation of infarction. It is still unknown whether the coagulation disruption is primarily caused due to viral activity or secondary due to the inflammatory response. Hemorrhagic transformation is a complication of ischemic stroke, particularly in post-thrombolysis patients. However COVID-19 coagulopathy was thought to induce such event in COVID-19 patients presented with ischemic stroke.

Conclusion: Although ischemic stroke has been widely reported in COVID-19 patients, there have been a few reports of hemorrhagic transformation events. This may lead to an increased understanding regarding COVID-19 pathophysiology and cerebrovascular disease.

Keywords: COVID-19, hemorrhagic transformation, stroke, coagulopathy.
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INTRODUCTION

Since December 2019, the novel coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus in Wuhan, China, has led to a pandemic with the death rate up to 7.8% in people aged 80 and over.[1] Although first considered as a primary respiratory infection, worldwide case reports have suggested that COVID-19 leads to systemic arterial and venous thrombosis through the prothrombotic state.[2–4] Ischemic stroke is one of the most common neurological manifestations of COVID-19 and has been widely reported.[5] However, there have been a few reports of the hemorrhagic transformation of infarction in COVID-19 patients.[6] Hereby, we are reporting two cases of hemorrhagic transformation in SARS-CoV-2 infected patients who were admitted in our hospital in Indonesia.

CASE 1

A 50-year-old lady was admitted due to shortness of breath for two days before admission, with frequent coughing. She had a history of contact with a suspected SARS-CoV-2 individual within the last two weeks. Her past medical history was hypertension and diabetes. Initially, she had preserved consciousness, BP 117/93 mmHg, HR 113 bpm, RR 34 pm, t 36.8oC, and oxygen saturation 94%. Her blood tests showed mild anemia (10.9 g/dL), thrombocytosis (477,000/mm3), azotemia (Ureum 90 mg/dL), mild hyponatremia (134 mmol/L), hyperglycemia (313 mg/dL), elevated CRP (13 mg/L), and acute respiratory distress syndrome-compensated respiratory acidosis on blood gas analysis. Chest X-ray showed bilateral bronchopneumonia with ground-glass pattern. She was admitted to the intensive care unit due to suspected COVID-19 pneumonia, severe ARDS, hyperglycemia on diabetes, and hypertension. On day 5, the SARS-CoV-2 PCR was positive and she was transferred to the intensive isolation ward treated with oseltamivir, azithromycin, and hydroxychloroquine regiments. On day 8, she developed sudden global aphasia, right hemiparesis, acute kidney injury, and atrial fibrillation which were treated promptly. Non-contrast head CT scan demonstrated extensive left frontal infarction in the left anterior cerebral artery territory without raised ICP signs (Figure 1a). Coagulation studies were within normal limits. On day 11 she was planned for continuous renal

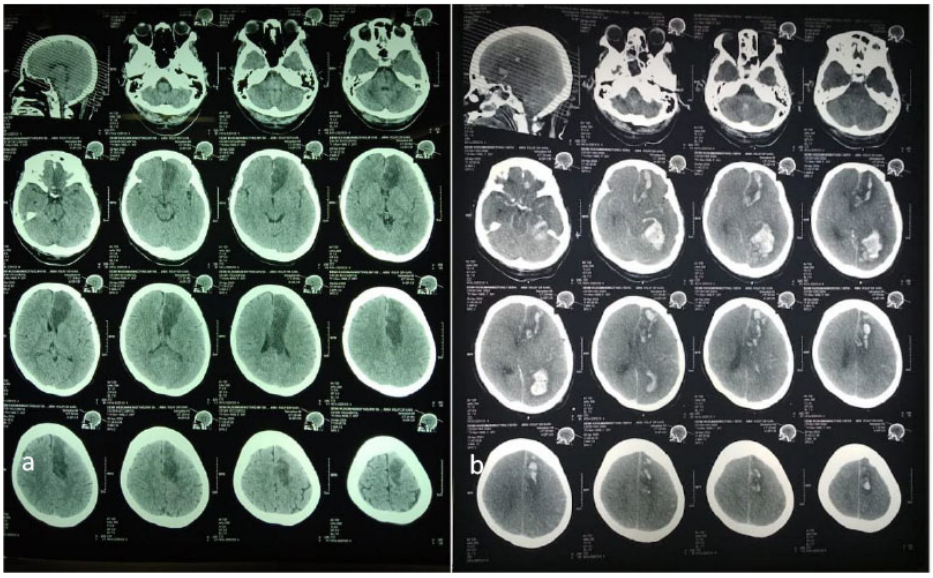

Figure 1. Non-contrast head CT Scan of patient 1 showing (a) extensive left frontal infarction in left anterior cerebral artery territory; (b) extensive hemorrhagic transformation on the site of infarction.

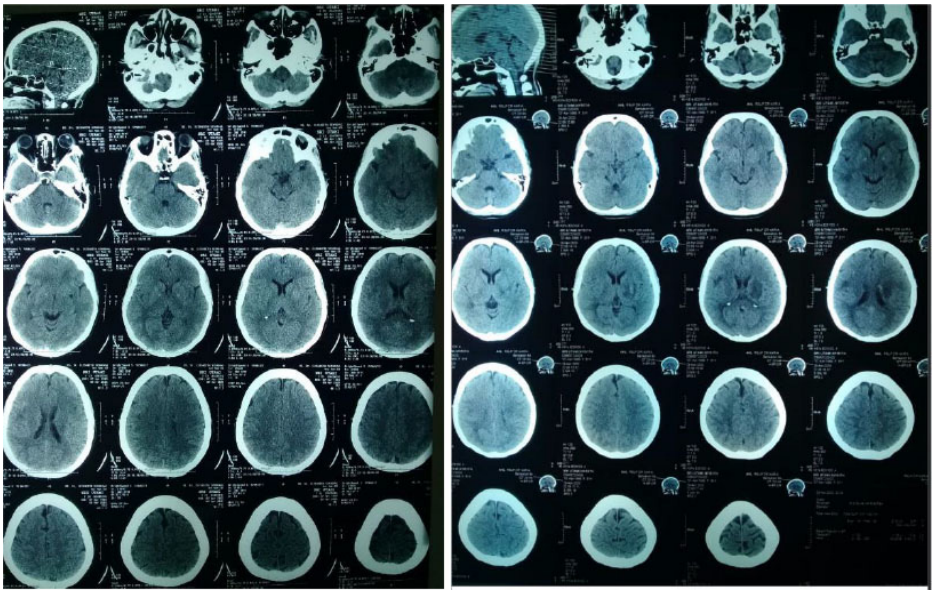

Figure 2. Non-contrast head CT Scan of patient 2 showing (a) left basal ganglia infarction; (b) hemorrhagic transformation on the site of left basal ganglia infarction with perifocal oedema and right frontal lobe infarction.

replacement therapy (CRRT) however her coagulation study result was prolonged thus the CRRT session was terminated. On day 13, she lost her consciousness and the repeated CT scan showed an extensive hemorrhagic transformation of infarction (Figure 1b).

CASE 2

A 51-year old lady was admitted to the emergency room with the chief complaint of post-wake-up sudden left-sided weakness, slurred speech, and unilateral face drop since a day before admission. Seizure, headache, and loss of consciousness were denied. She also complained of cough although fever was denied. Two weeks before admission she was hospitalized for right-sided weakness and diagnosed with ischemic stroke (Figure 2a). Past medical history was heart failure due to ischemic heart disease and hypertension. She was under aspirin, isosorbide dinitrate, carvedilol, candesartan, and spironolactone. She denied fever although complained of frequent coughing. Physical examination demonstrated preserved consciousness, BP 130/58 mmHg, HR 49 bpm, RR 30 pm, T: 36.9oC, and oxygen saturation 92%. Neurological examination showed central 7th and 12th nerve palsies, spastic bilateral paresis, and negative meningeal signs. Blood tests revealed serum hyponatremia (117.0 mmol/L), hyperkalemia, (6.1 mmol/L), azotemia (261 mg/dL) and hypercreatininemia (4.7 mg/dL), while urine examination revealed increased bacteria count (>99,000 µ/L). Her coagulation studies were prolonged. Head CT Scan showed an intracerebral hemorrhagic transformation of infarct at left basal ganglia with perifocal edema without signs of raised ICP and infarct on right frontal lobe (Figure 2b). The chest X-ray revealed bronchopneumonia and elongated aorta while ECG revealed atrioventricular block grade II. She was then admitted to the stroke unit under the diagnosis of hemorrhagic transformation, electrolyte imbalance, chronic kidney disease, atrioventricular block grade II, and urinary tract infection which were treated promptly.

DISCUSSION

Ischemic stroke has been demonstrated as a common neurological manifestation of COVID-19 and also the most common form of cerebrovascular diseases (85%) in COVID-19 patients.[7] COVID-19 is also thought to be associated with strong inflammatory reaction characterized by increased IL-1, IL-6, and TNF-α leading to raised D-dimer levels and high occurrence of antiphospholipid antibodies creating a prothrombotic state.[8] In COVID-19 patients, the coagulation profile included mild prolongation of prothrombin time, activated partial thromboplastin time, and mild thrombocytopenia.[8,9] Several authors have suggested that endothelial damage after SARS-CoV-2 infection in the lung arterioles and capillary might be correlated with the incidence of disseminated intravascular coagulation, deep vein thrombosis, and pulmonary embolism. This was supported by the

autopsy report in the SARS-CoV patient had revealed multiple-organ thrombosis.[10] Recent findings showed that SARS-CoV-2 infected patients tended to develop severe hypercoagulability rather than consumptive coagulopathy supported by the increased serum fibrinogen levels and fibrin polymerization.[11] Although both viruses were structurally similar, it remains unclear whether the thrombotic complication present in the SARS-CoV-2 infection were similar to the deranged coagulation cascade presented in the SARS-CoV infection.

Besides thrombosis, intracranial hemorrhage (ICH) was also reported in COVID-19 patients either as primary ICH or hemorrhagic transformation.[12] Although the mechanism is unclear, SARS-CoV-2 infection is thought to cause spontaneous intracerebral bleeding by endothelial dysfunction due to binding to the angiotensin-converting enzyme-II (ACE-II) receptor in the CNS and leading to disrupted autonomous regulation and increased blood pressure.[13] Moreover, hypoxia-induced blood-brain barrier disruption either due to COVID-related acute respiratory failure or microvascular thrombosis due to prothrombotic state in COVID might also be responsible as an underlying pathophysiology.[14] Disruption of the blood-brain barrier has been proposed as an important underlying feature of hemorrhagic transformation in animal models and non-COVID patients.[15] Besides rt-PA thrombolysis, other clinical factors such as age, hypertension, hyperglycemia, genetics, unfavorable imaging findings, and the use of anticoagulants or antiplatelets were also correlated with increased risk of hemorrhagic transformation.[16] In rt-PA thrombolysis cohort, early fibrinogen degradation coagulopathy was a predictor for a worse outcome, with reduced fibrinogen level and increased fibrinogen degradation product (FDP) level predicted higher risk of early hemorrhage after rt-PA therapy.[17] In contrary, fibrinogen level was raised in SARS-CoV-2 patients, therefore the mechanism of hemorrhagic transformation in both conditions might be different.

A report regarding hemorrhagic transformation in SARS-CoV-2 patients with malignancy demonstrated that both SARS-CoV-2 and malignancy might contribute in hypercoagulability state and thrombocytopenia which seemed paradoxical.[18,19] In our series, both patients had prolonged coagulation panel characteristic of COVID-19, however the first patient had thrombocytosis instead of thrombocytopenia. One patient consumed antiplatelet after an episode of infarction which might increase her susceptibility for hemorrhagic events. However, both patients did not receive thrombolysis and anticoagulants. Therefore, coagulation function derangement possibly induced by SARS-CoV-2 infection might lead to the occurrence of hemorrhagic transformation which was promptly managed. Although the exact mechanism between hemorrhagic transformation and COVID-19 has not been elucidated, our report might add the literature regarding the possibility of COVID-19 related hemorrhagic events that might be related to coagulation disruption.

CONCLUSION

We are reporting the cases of hemorrhagic transformation in SARS-CoV-2 infected patients in Indonesia. We emphasize the importance of recognizing acute neurological manifestation in suspected COVID-19 patients and the possibility of deranged coagulation state leading to thrombosis and hemorrhage. We would also highlight the possibility of SARS-CoV-2 infection as a possible risk factor of hemorrhagic transformation in stroke patients. This report should add the literature to further discover the relationship between COVID-19 and cerebrovascular diseases.

CONFLICT OF INTEREST

None.

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ETHICAL CONSIDERATION

Patient/legal guardian had received signed written informed consent regarding publication of their medical data in journal article.

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