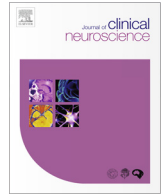




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Correspondence

Predictors of intracerebral hemorrhage in COVID-19

Yoshimi Shinohara^a, Ryo Miyaoka^{a,*}, Makoto Hirose^b, Junkoh Yamamoto^a^a Department of Neurosurgery, School of Medicine, University of Occupational and Environmental Health, Kitakyusyu, Japan^b Department of Hematology, School of Medicine, University of Occupational and Environmental Health, Kitakyusyu, Japan

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Dear Editor,

We read with interest the case series regarding intracranial hemorrhage in COVID-19 by Fayed et al. [1]. Except for hemorrhagic infarction, the other two cases have backgrounds of underlying diseases with antiplatelet therapy, developed intracranial hemorrhage in the context of anticoagulation. They have undergone a severe clinical course for more than a week before the identification of bleeding. From their situation of respiratory failure and high D-dimer, it is presumed that they have been in a COVID-19-associated coagulopathy (CAC) state that could cause pulmonary embolism and pulmonary epithelial thrombosis [2].

CAC is being used to describe the coagulation changes in COVID-19 and characterized by the early coagulation dysfunction as a risk factor for thromboembolism. The prognosis improved by anticoagulation therapy during the early phase of COVID-19. Therefore, it has been recommended to begin the anticoagulation therapy based on the coagulation test screening [3].

We experienced a case of COVID-19 that followed a similar clinical course. A 79-year-old male with a history of myelodysplastic syndromes (MDS) on immunosuppressant and coronary artery stenosis status on aspirin was transferred to the emergency department with severe respiratory failure. Blood tests showed high inflammatory states and acute renal dysfunction. After testing positive for SARS-CoV-2, he was diagnosed co-infection with bacterial pneumonia and SARS-CoV-2. Since his high D-dimer and Sepsis-induced coagulopathy (SIC) score was 4, he was diagnosed CAC

and started a heparin drip based on the current medical consensus [3,4]. The heparin level remained within the control range, in addition to his home dose of aspirin. On the seventh day of hospitalization, he suddenly presented with right hemiparesis and sensory disturbance, and left intracerebral hemorrhage (ICH) was revealed by an urgent computed tomography (CT) (Fig. 1A). Diagnostic workup was completed with magnetic resonance imaging (MRI) later, but did not show any underlying pathology for the origin (Fig. 1B).

Two hypotheses were proposed as the pathogenesis of ICH in COVID-19 patients. As the author advocate, one is the direct invasion of SARS-CoV-2 into the central nervous system (CNS), which is assumed due to retrograde transfer via peripheral nerve [5,6]. The other is the endotheliopathy, which has been proposed various hypothesis about the mechanism. One is that viral replication inducing inflammatory cell infiltration and apoptosis of endothelial cells [7]. Another hypothesis is the consequence of massive inflammatory effects under the cytokine storm as observed in patients with sepsis resultant prothrombotic properties [3].

Because we and the authors did not detect any focal deficit or imaging findings in the cases, it is suggested that endotheliopathy is more suspicious as the mechanism of bleeding than CNS viral infiltration. Interestingly, our case had a background of immunosuppressive therapy for MDS and co-infection with bacterial pneumonia. Since the immunosuppressive state that could suppress cytokine storms but induce hyper viremia, the mechanism of endotheliopathy due to intracellular proliferation of SARS-CoV2 could be presumed.

To the best of our knowledge, there were 15 cases of 9 reports ([1,5,8–13] and our case) of COVID-19 associated with ICH, those with the particulars of the clinical course (Supplementary Table 1).

* Corresponding author: Department of Neurosurgery, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu 807-8555, Japan.

E-mail address: 38spec@med.uoeh-u.ac.jp (R. Miyaoka).

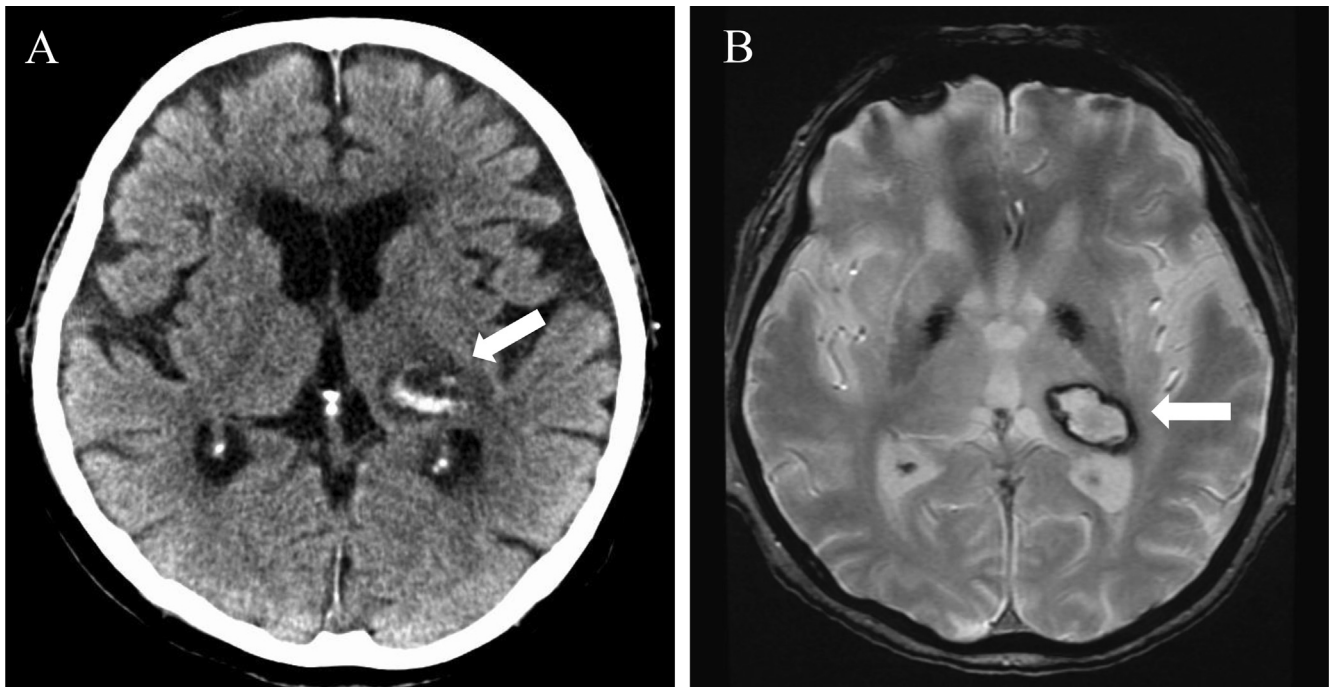


Fig. 1. Head CT and MRI images of the patient (axial scans). (a) Head CT images on the day of right hemiparesis presentation. CT images showed acute intracerebral hemorrhage with fluid-blood level (arrow) in left basal ganglia. (b) Follow-up MRI images demonstrate hematoma in left thalamus with evidence of chronic hemorrhage indicated by hyperintense lesion with hypointense rim (arrow) on T2* images.

The average time between onset of initial symptoms and ICH identification was 20.4 days. 13 of 15 (87%) patients were on anticoagulant therapy, and concomitant antiplatelet therapy was observed in 31%. Along with respiratory dysfunction, 92% presented renal dysfunction (defined as creatinine > 1.2 mg/dl or description suggesting the condition) and 40% were undergoing hemodialysis.

It is capable of being anticipated that anticoagulation affects the onset of ICH. Our case was identified with irregular shaped hematoma, the characteristic finding of the ICH containing fluid-blood level, which has a high specificity for patients with anticoagulation [14]. In terms of monitoring proper anticoagulant therapy, it is suggested that following anti-FXa activity besides aPTT measurements should be considered, because CAC-induced hyperfibrinogenemia may cause both hypercoagulability and heparin resistance [3]. Surprisingly, 87% were not measured anti-FXa activity at time of ICH. In these reports, possibly including cases of iatrogenic bleedings due to unstable control of coagulation function because of concurrent renal dysfunction.

An important point to emphasize is that ICH, an uncommon complication in patients of COVID-19, can be induced by long-term anticoagulation. Therefore, we should pay attention to maintain the proper therapeutic range and consider early termination of anticoagulation, especially in cases with renal dysfunction. In addition, it may be necessary to accumulate cases of concomitant use with antiplatelet drugs and consider reviewing the current medical consensus.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jocn.2021.01.031>.

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