Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 193 (2020) 22–24

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

A case of COVID-19 pneumonia with cerebral hemorrhage

Dear Editor,

We agree with Dr. Klok that thromboprophylactic dose low molecular weight heparin should be recommended for all the critically ill patients with 2019 novel coronavirus disease (COVID-19) pneumonia [1]. The very high cumulative incidence of thrombotic complications raises the question if therapeutic anticoagulation should be considered for severe COVID-19 pneumonia patients. As previously reported, patients with COVID-19 may show a wide range of neurologic manifestations, such as loss of consciousness, headache, seizures, ageusia, hyposmia and dysphagia. When clinicians evaluate patients with neurologic symptoms, they should consider SARS-CoV-2 infection as a differential diagnosis [2]. The most commonly described clinical features of COVID-19 have related to overwhelming respiratory symptoms and neurological symptoms have been underestimated and under-reported [3,4]. Recently, Ling Mao and colleagues showed that among 214 COVID-19 patients, 2.8% of them had ischemic stroke [2]. Here we present a case of COVID-19 pneumonia with cerebral hemorrhage. We propose that cerebral hemorrhage, in addition to ischemic stroke, can be a severe neurological manifestation in COVID-19 patients.

A 68-year-old male patient with a history of atrial fibrillation on long-term warfarin presented with fever, cough and fatigue for 8 days, associated with shortness of breath for 5 days. He was admitted on Feb 5th, 2020 [illness day 8 (iDay) 8] to Wuhan Red Cross Hospital, a hospital designated to treat patients with severe COVID-19. The patient reported that he had been in contact with confirmed COVID-19 patients. His oropharyngeal swab was tested positive for SARS-CoV-2 by reverse-transcription polymerase-chain-reaction (RT-PCR) assays. No other respiratory viral pathogens were detected. His chest CT showed bilateral multifocal ground-glass opacities, consistent with of COVID-19 pneumonia. The laboratory results indicated elevated INR (1.6), prolonged PT (14.5 s) and normal creatinine (65 μmol/L). He had high levels of both D-dimer (70 mg/L), and C-reactive protein (77.6 mg/L). The patient was diagnosed with severe COVID-19 pneumonia and was admitted to ICU. His oxygen saturation (SpO2) decreased to 80% and he was started with non-invasive mechanical ventilation. He received supportive care; anti-viral treatment including arbidol (0.2 g, tid), lopinavir with ritonavir (LPV/RTV, 400 mg, bid) and recombinant human interferon beta-2b injection (5 million iu, qd); anti-bacterial treatment including moxifloxacin (250 mL, iv drip, qd); and low dose glucocorticoid treatment including methylprednisolone sodium succinate (MPSS, 40 mg, iv drip). Meanwhile, his warfarin was discontinued and he was started with subcutaneously treatment of low molecular weight heparin (LMWH, 4100 iu, qd; nadroparin calcium, AOSIDA, Hebei Changshan Biochemical Pharmaceutical Co., Ltd., 0.4 mL: 4100 iu; his weight 62 kg) for his atrial fibrillation.

On iDay 12 (Feb 9th, 2020), he became somnolent and his oxygen saturation decreased to 47%. He was emergently intubated and was started with invasive mechanical ventilation. He was aggressively treated for COVID-19 pneumonia and acute respiratory failure with hypoxia/ARDS. On iDay 19, the patient experienced altered consciousness and his blood pressure rose up to 154/86 mm Hg after titrating off sedatives for the daily awakening trial. The laboratory results indicated elevated creatinine (179.1 μmol/L), elevated D-dimer (10.99 mg/L), INR (2.06) and prolonged PT (24.1 s). Thus he had CT scans of head and chest. Head CT images showed right temporal occipital lobe and left frontal occipital parietal lobe hemorrhage with extension to bilateral lateral ventricles (especially on the right), subarachnoid hemorrhage and brain herniation (Fig. 1D–F). Chest CT images showed progressive bilateral ground glass opacities compared with the previous CT at admission (Fig. 1A–C). Additionally, we ran viral antibody tests of SARS-CoV-2 reactive IgM/IgG (INNOVITA Biotechnology Company; Chengdu precision medicine industrial technology research institute co. LTD of west China) and got positive results for both IgM and IgG. These results indicated that after more than 3 weeks of illness, his immune system had started to respond to the SARS-CoV-2 virus but the infection was not yet cleared.

For the treatment of cerebral hemorrhage, mannitol was given to reduce the intracranial pressure and cerebral edema. He had progressive bilateral ground glass opacities and possible superimposed bacterial infection despite antibiotics and so these were changed to cefoperazone sulbactam (1.5 g, iv drip, qd). He continued to have progressive multi-organ failure with worsening respiratory failure and renal failure. After being comatose for one week, he had cardiopulmonary arrest and died on iDay 26.

This is, to our knowledge, the first case to report a COVID-19 patient with a complication of cerebral hemorrhage. Hypertension is the most common cause of cerebral hemorrhage [5]. Coagulopathy remains a common cause of cerebral hemorrhage [6]. Our patient had been on long-term warfarin due to atrial fibrillation, which was switched to the therapeutic dose of LMVH after admission. We started with LMVH 4100 iu per day, given the elevated INR of 1.6 and prolonged PT of 14.5 s. We planned to increase the dose to 4100 iu bid with continuous monitoring of his INR. However, he continued to have elevated INR of 2.06 and prolonged PT from 18.7 s to 24.1 s in the next days. Thus, we were not able to increase LMWH dose as we planned. Unfortunately, he had a cerebral hemorrhage. We speculated that the SARS-CoV-2 induced cytokine storm contribute to the progressive multi-organ failure, and may also contribute to cerebral hemorrhage for this patient. Anticoagulation might aggravate his cerebral hemorrhage [7,8].

This case indicates the complexity of COVID-19 comorbidity. Changes in neurological status should raise our awareness for further

https://doi.org/10.1016/j.thromres.2020.05.050
Received 13 May 2020; Received in revised form 28 May 2020; Accepted 28 May 2020
Available online 30 May 2020

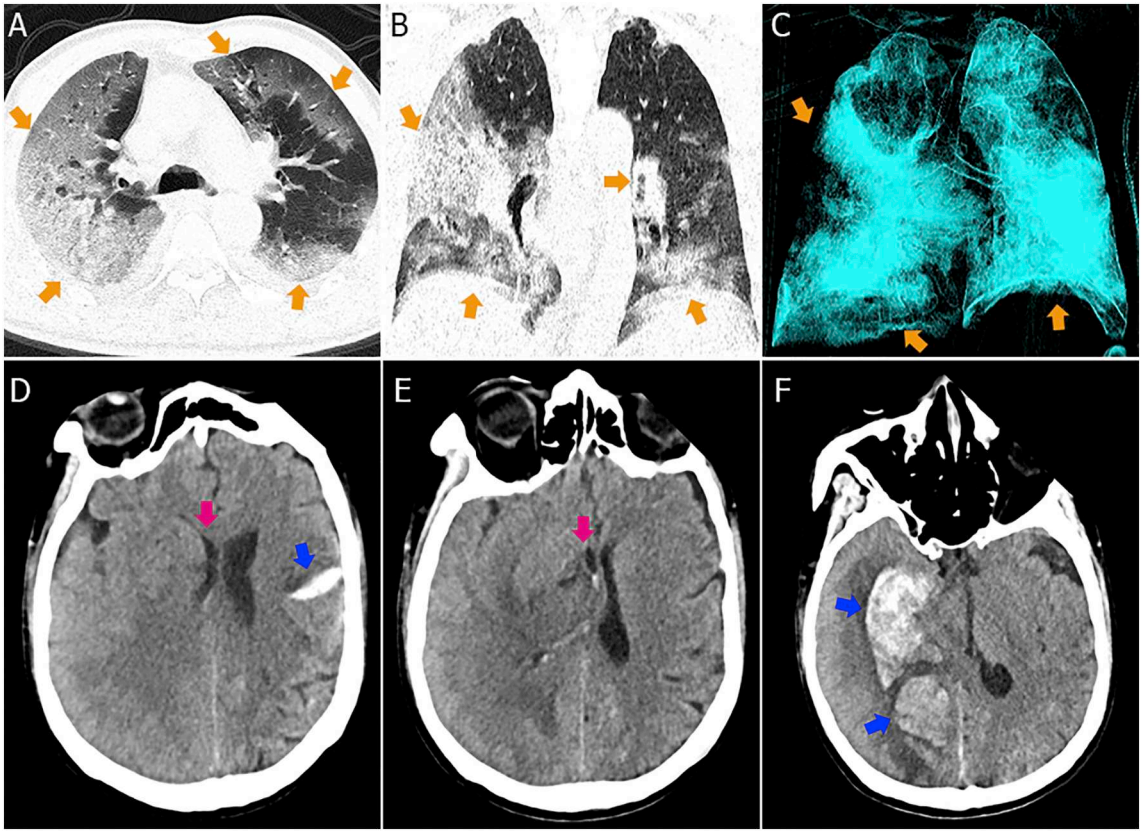

Fig. 1. Chest and head CT images of the COVID-19 patient. (A, axial chest CT scan; B, coronal chest CT scan; C, chest CT image of volume rendering technique; D–F, head CT scans.)
(A–C) Chest CT images showed bilateral sporadic ground grass opacities (marked by orange arrows), right lung prominent with air bronchogram sign. Small amount of effusion was under bilateral pleura. (D–F) Head CT showed high density hemorrhage of bilateral temporal lobe and right occipital lobe with peripheral edema (blue arrows). Right ventricle was obviously compressed with narrowed sulci and gyri (purple arrows), and brain midline was slightly shifted to the left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

work up. Cerebral hemorrhage could contribute to COVID-19 mortality. Clinicians need to consider neurological manifestations of COVID-19, including ischemic stroke and cerebral hemorrhage. Clinicians need to monitor the mental status with daily awakening trial for patients on invasive mechanical ventilation. We also need to weight the benefits and risks for anticoagulation treatment in COVID-19 patients.

Author contributions

JwL, XL, CZ, SH and NX collected the epidemiological and clinical data and processed statistical data. JwL, XL and CZ drafted the manuscript and share first authorship. NX, ZL and JhL revised the final manuscript. NX is responsible for summarizing all epidemiological and clinical data.

Funding

This work was supported by the National Key Research and Development Program of China [grant numbers 2016YFC1306600 and 2018YFC1314700], the National Natural Science Foundation of China [grant number 81873782], all to NX.

Ethical approval

This study was approved by the Ethics Committee of the Wuhan Red Cross Hospital.

Patient consent

Obtained.

Declaration of competing interest

None to declare.

References

[1] F.A. Klok, M. Kruip, N. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F. Kaptein, J. van Paassen, M. Stals, M.V. Huisman, H. Endeman, Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients

with COVID-19: an updated analysis, Thromb. Res. 191 (2020) 148–150.
[2] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, et al., Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China, Jama Neurol (2020), https://doi.org/10.1001/jamaneurol.2020.1127.
[3] L. Zhou, M. Zhang, J. Gao, J. Wang, Sars-Cov-2: underestimated damage to nervous system, Travel Med. Infect. Dis. 101642 (2020).
[4] A. Bersano, L. Pantoni, On being a neurologist in Italy at the time of the COVID-19 outbreak, Neurology 94 (21) (2020).
[5] J.T. Haller, A.L. Wiss, C.C. May, G.M. Jones, K.S. Smetana, Acute management of hypertension following intracerebral hemorrhage, Crit. Care Nurs. Q. 42 (2019) 129–147.
[6] A.I. Qureshi, S. Tuhrim, J.P. Broderick, H.H. Batjer, H. Hondo, D.F. Hanley, Spontaneous intracerebral hemorrhage, N. Engl. J. Med. 344 (2001) 1450–1460.
[7] T. Steiner, M. Kaste, M. Forsting, D. Mendelow, H. Kwiecinski, I. Szikora, S. Juvela, A. Marchel, R. Chapot, C. Cognard, et al., Recommendations for the management of intracranial haemorrhage - part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee, Cerebrovasc. Dis. 22 (2006) 294–316.
[8] A.D. Mendelow, Spontaneous intracerebral haemorrhage, J. Neurol. Neurosurg. Psychiatry 54 (1991) 193–195.

Jingwen Li[a,1], Xi Long[b,1], Chunli Zhu[c,1], Shaoping Hu[d], Zhicheng Lin[e,2], Jinghong Li[f,*], Nian Xiong[a,c,**,2]

[a] *Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[b] *Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China*
[c] *Department of Neurology, Wuhan Red Cross Hospital, Wuhan, Hubei, China*
[d] *Department of Radiology, Wuhan Red Cross Hospital, Wuhan, Hubei, China*
[e] *Laboratory of Psychiatric Neurogenomics, McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA*
[f] *Department of Medicine, University of California San Diego, La Jolla, CA 92093, USA*

E-mail addresses: jil055@health.ucsd.edu (J. Li), nianxiong@hust.edu.cn (N. Xiong).

[*] Corresponding author.
[**] Correspondence to: N. Xiong, Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1227 Jiefang Ave, Wuhan, Hubei, China; President of Wuhan Red Cross Hospital, 392 Hongkong Road, Wuhan, Hubei, China.
[1] These authors contribute equally to this work.
[2] Joint last coauthor.