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CASE REPORT

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Clinical patterns of endothelial damage and thrombotic events in two patients with COVID-19: A case report

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Abstract

Endotheliopathy causes COVID-19 conflicting complications.

KEYWORDS

blood coagulation disorders, COVID-19, endothelial cells

1 | INTRODUCTION

In this study, two patients with probability of endothelial damage and different clinical manifestations of COVID-19 were presented. It seems that besides increasing coagulation, the main cause of these events can probably be endothelial damage.

Vascular dysfunction associated with COVID-19 usually manifests in several forms, including deep venous thrombosis, pulmonary embolism, large arterial thrombosis, multiorgan venous, and arterial thrombosis. These manifestations have been attributed to some factors such as hypoxemia, viral sepsis, immobility, and occasionally vasculitis.[1] Early autopsy studies documented respiratory failure due to acute respiratory distress syndrome(ARDS), which is frequently accompanied with capillary micro thrombosis, superimposed bronchopneumonia, pulmonary thromboembolism, and signs of multiorgan failure with shock organs that is known as a predominant cause of death.[2] Recent evidence in this regard suggested that signs and symptoms of severe COVID-19 infection mimic clinical features of endothelial dysfunction and share some mutual pathophysiological mechanisms.[3] Other proposed pathophysiological pathways of COVID-19 are endothelial cell damage due to ACE2-mediated entry of SARS-CoV-2, which subsequently cause inflammation and the generation of a prothrombotic setting. Of note, the peptidase ACE2 is found on the surface of alveolar epithelial, small intestinal epithelial, vascular endothelial, arterial smooth muscle, immune cells, and neurons.[4,5] Accordingly, this phase of the disease is consistent with the belief stating that COVID-19 is associated with severe endothelial cell inflammation contributing to cardiovascular complications. It is important to note that the severity of the condition can strongly depend on each patient's characteristics, including incidences of comorbidity (particularly inflammatory conditions such as cancer and diabetes).[6] It seems that there is endothelial damage, which is considered as a common occurrence in all patients with severe COVID-19; however, the characteristics of the patient who develops thrombotic events or bleeding also are important issues.

2 | CASE DESCRIPTION

In this study, two patients with COVID-19 were evaluated. The patients' characteristics at baseline are shown in Table 1.

Patient 1 was a 63-year-old woman with no past medical history presented with the decreased level of consciousness. Family members of this patient mentioned that she had been exposed to a COVID-19 patient in the last few

TABLE 1 Laboratory tests of patients in admission

	WBC	HB	PLT	Lymph	CRP(NL <5mg/l)	LDH(NL<250 u/l)	INR
Patient 1	20 900	16.5	304 000	3803	97	634	1
Patient 2	72 900	15.6	187 000	59 778	5	533	1

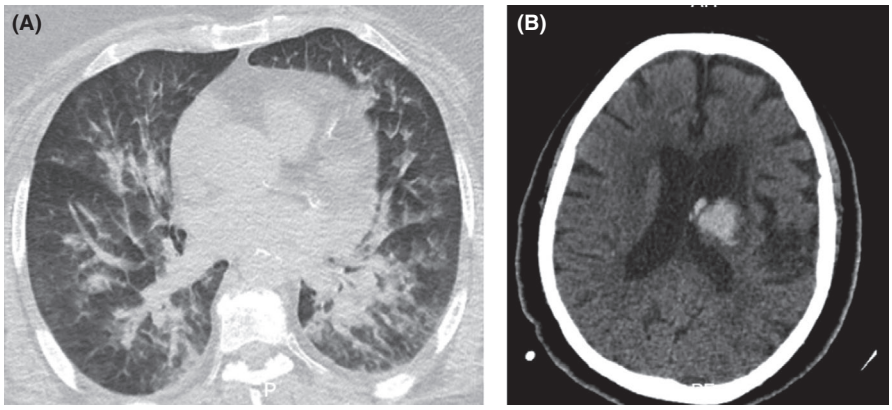

FIGURE 1 A, Lung Spiral CT scan of patient, that show difuse ground glass opacity suggested of COVID-19. B, Brain CT scan of patient 1, that show intracranial hemorrahge

days. Of note, the patient has been experiencing shortness of breath and fever within 3 days before admission. On her admission day, the severeness of shortness of breath was progressive, accompanied by chest pain. One hour before arriving the emergency department, she has agitated and subsequently lost her consciousness. Her vital signs were as follows: Blood Pressure: 220/140, O_2Sat: 78%, RR: 32, BT:38/5, and PR:130. A bilateral fine crackle was heard in her lung examination. Due to the decreased levels of consciousness and oxygen saturation, she was immediately intubated. Brain CT scan showed an evidence of intracerebral hemorrhage (ICH), (Figure 1B), and lung CT was also performed, (Figure 1A). Because of the clinical features of both heart failure and *pulmonary edema*, cardiologists began infusional nitroglycerin and furosemide. According to the history and evidence of suspected ground-glass opacity (which is not fully justified by pulmonary edema) suggested by the patient's CT scan result, a rapid RT-PCR of COVID-19 was sent, which was reported positive. Additionally, the qualitative troponin was positive. The ECG showed tachycardia with normal sinus rhythm and no ST-T change. The level of troponin in the quantitative assay was estimated as 25 205 pg/ml(up to 15.6). Echocardiography evaluation of ejection fraction was 45%, and myocarditis was diagnosed for this patient. Therefore, dexamethasone, interferon, and remdesivir were administered. Thereafter, anti-infiltrative drugs such as vitamin C, zinc, and famotidine were prescribed. With neurosurgery consultation, surgery was not required and the patient was supervised by neurologist, infectious, and cardiac specialists. Unfortunately, the patient died after two days because of massive lung involvement.

Patient 2 was a 67-year-old man with a history of hypertension(HTN) who was smoking 20 *pack* per *year*. Three months before his admission, in routine examinations and laboratory tests, he had shown signs of leukocytosis with lymphocyte-predominant, normal hemoglobin, and platelets. Moreover, on his examinations, there was bilateral lymphadenopathy in the neck and axillary, and the spleen was palpated three centimeters below the costal margin. As well, B-Cell chronic lymphocytic leukemia (B-CLL) was confirmed by flow cytometry, and the cytogenetic study was normal. Only follow-up was determined to be necessary because the patient obtained the second stage in Rai. Weakness and weight loss began by passing three months from the CLL diagnosis, and RT-PCR COVID-19 was positive in his evaluation. Due to brief symptoms, hospitalization was not needed and the patient was only followed-up. Notably, he lost five kilograms of weight during one month, and CBC was as same as before. The patient showed no new findings on the examinations, so he was hospitalized again to find the cause of weight loss. Thereafter, flow cytometry was sent again to check the CLL status. An axillary lymph node biopsy was performed, all of which showed the same CLL disease with no changes in its nature. The only new finding in lung and abdominopelvic CT scans was bilateral pulmonary emboli (Figure 2). Color doppler ultrasound for deep vein thrombosis (DVT) was negative. Furthermore, blood test results for antiphospholipid syndrome were negative, and prostate-specific antigen (PSA) was normal. Endoscopic and colonoscopic were deemed to be necessary due to epigastric pain and weight loss, the results of which were normal. In lung CT, besides embolism, there was an evidence of COVID-19 involvement, so anticoagulation therapy (Enoxaparin 60 mg every 12 hours) was started, and the patient was followed-up because of his stable condition. One month later, weight loss stopped, anticoagulants were received, and his weakness has disappeared.

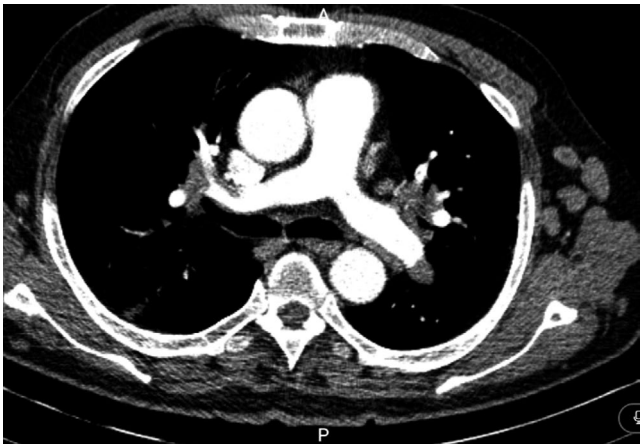

FIGURE 2 Lung CT Angiography of patient 2

3 | DISCUSSION

In this study, neither the patient with ICH had any underlying disease nor the patient with CLL had any active disease. Previously published articles in this regard have reported thromboembolic complications and ICH due to COVID-19 [7] ; however, the differences between these reports were concurrent myocarditis and cerebral hemorrhage in one patient. Accordingly, this may probably represent endothelial damage prominency and massive thromboembolism in another patient, indicating hypercoagulability state. The cause of endothelial damage cannot be related to any underlying disease; therefore, COVID-19 was determined as the main cause. It is well known that endothelial cell injury can activate the coagulation system via exposure to tissue factor and other pathways.

Therefore, it can be said that COVID-19 infection aggravates endothelial dysfunction and then generates a hypercoagulable state. In a meta-analysis consisting of 23 studies conducted on 148 patients by Cheruiyot et al, the incidence rate of cerebral hemorrhage was reported to be 0.7%, especially in patients with underlying diseases like HTN. Interestingly, during our evaluation, no underlying disease was found and the only finding was focal hemorrhage in brain CT.[8] The study by Benger et al presented five patients with ICH and COVID-19 whose Brain CT scan findings were focal. Among them, two cases had no history of anticoagulant use, similar to our patient.[9] But to answer what leads one patient to present with bleeding and the other with thrombosis manifest, we can say that in some cases, DIC (disseminated intravascular coagulation) might occur with fulminant COVID-19 lung disease, which is also characterized by diffuse thrombosis and hemorrhaging. Exclusion of both DIC and large-vessel thrombosis makes it clear that patients with severe COVID-19 pneumonia can also show some signs of severe skin vasculitis-like changes, suspected cerebral vasculitis, and multiorgan failure whereby viral endothelium, direct viral infection or vasculitis are suspected.[10] A study was conducted on 68 patients with COVID-19, who were divided into the following two groups: 48 patients were admitted to the ICU, and 20 others to the ward. For all these patients, some tests including VWF (Von Willebrand factor), PAI-1, soluble thrombomodulin, soluble P-selectin, and sCD40L were conducted. They found that epitheliopathy and platelet activation might be important factors in the pathophysiology of COVID-19-associated coagulopathy.[11] In the current research, we tried to share our findings of two patients with no underlying diseases who had no reason to justify the widespread acute embolism and bleeding. It is interesting to note why bleeding is predominant in one patient with COVID-19, and thrombosis is predominant in another.

4 | CONCLUSION

The essential problem in COVID-19 is endothelial damage, causing a wide range of clinical manifestations. Given that the role of anticoagulants in the treatment of COVID-19 is highlighted, so paying attention to the clinical hemorrhagic pattern of COVID-19 endothelial damage is considered as a key point.

ACKNOWLEDGMENTS
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CONFLICTS OF INTEREST
There are no conflicts of interest.

AUTHOR CONTRIBUTIONS
MM, KK, and MS: equally contributed in designing, reviewing, drafting, analyzing the data, and writing the manuscript.

ETHICAL STATEMENT
For publishing this case report, we asked Valiasr hospital ethical committee for approval.

DATA AVAILABILITY STATEMENT
No data were obtained for this case report.

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