CASE REPORT OLGU SUNUMU

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Deep Vein Thrombosis Despite Anticoagulant Therapy in a Patient with COVID-19-Related Hemorrhagic Stroke

COVID-19 İlişkili Hemorajik İnmeli Hastada Antikoagülan Tedaviye Rağmen Derin Ven Trombozu

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ABSTRACT Coronavirus disease-2019 (COVID-19) is a viral infection caused by the severe acute respiratory syndrome-coronavirus-2 and was declared a global pandemic by the World Health Organization on March 2020. Although COVID-19 mainly effects the respiratory system, it is a multisystem disease and neurological involvement may also occur. In this case, we reported a patient with COVID-19-related hemorrhagic stroke and indicated the development of deep vein thrombosis despite anticoagulant therapy and ambulation of the patient in the stroke rehabilitation process. The risk of venous thrombosis may be high in COVID-19-related stroke due to the thrombogenic effect of COVID-19.

Keywords: COVID-19; hemorrhagic stroke; anticoagulant therapy; deep vein thrombosis

ÖZET Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], şiddetli akut solunum sendromu-koronavirüs-2'nin neden olduğu viral bir enfeksiyondur ve Dünya Sağlık Örgütü tarafından Mart 2020'de pandemi olarak ilan edilmiştir. COVID-19 esas olarak solunum sistemini etkilemekle birlikte multisistem bir hastalıktır ve nörolojik tutulum da görülebilir. Bu olgu sunumunda, COVID-19 ilişkili hemorajik inme hastasında rehabilitasyon sürecinde antikoagülan tedavi kullanımı ve ambulasyona rağmen derin ven trombozu gelişimini sunduk. COVID-19'un trombojenik etkisinden dolayı COVID-19 ilişkili inmede venöz tromboz riski yüksek olabilir.

Anahtar Kelimeler: COVID-19; hemorajik inme; antikoagülan tedavi; derin ven trombozu

Coronavirus disease-2019 (COVID-19) have been affected millions of people worldwide and several stroke cases have been observed with COVID-19.[1-4] Approximately 5% of COVID-19 cases treated in hospitals have a stroke and more than 80% of them are ischemic stroke. Few cases of COVID-19-related hemorrhagic stroke have been reported.[1,2] The relationship between COVID-19 and hemorrhagic stroke is controversial. COVID-19 can directly reach the central nervous system through the olfactory receptors of the 1st cranial nerve located in the nasal cavity cell membrane.[3] Most of the COVID-19 related strokes are commonly classified as cryptogenic.[2] In ischemic stroke that develops in COVID-19, vascular endothelial damage directly caused by the virus and hypercoagulation state that is responsible for infection-related cytokine storm are accused.[5] Despite this, the pathogenesis of hemorrhagic stroke in COVID-19 has not been fully explained. The virus may damage the intracranial arteries and cause vessel wall rupture via angiotensin converting enzyme II receptors in the arterial smooth muscle cell. The cytokine storm accompanying COVID-19 may cause intracerebral haemorrhage by destroying the blood-brain barrier and severe hypoxia developing during the course of infection, negatively affecting cerebral au-

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toregulation.[6] Another hypothesis is that coagulopathy caused by prolonged prothrombin time, thrombocytopenia, and increased D-dimer levels in COVID-19 increases the risk of intracranial haemorrhage (ICH).[7]

In the literature, the role of anticoagulants for the prevention of venous thromboembolism (VTE) in hemorrhagic stroke has been investigated and it has been reported that anticoagulant treatment (low-dose subcutaneous low molecular weight heparin) was safe in patients with ICH.[8-10]

CASE REPORT

A 51-year-old male patient with the diagnosis of COVID-19-related stroke was referred from intensive care unit (ICU) to the physical medicine and rehabilitation (PMR) service after a total of 55 days had passed since COVID-19 positivity. In the history of patient, during the ICU period, immune plasma, glucocorticoids, anti-cytokine, antiplatelet (clopidogrel 75 mg daily) and anticoagulant treatment (enoxaparin 60 mg bid) were given. The patient was found with left-sided hemiplegic while being extubated. Brain computed tomography showed ICH (2 hematomes in the right cerebellar hemisphere and one hematome in the right parietal lobe and millimetric parenchymal hematoma areas on the right thalamus) (Figure 1, Figure 2). Antiplatelet treatment was discontinued when ICH was noticed, and therapeutic anticoagulation (enoxaparin 60 mg bid) was continued in the same dose. The patient came to the PMR service with an immobilized functional status. His medical history was unremarkable. In his family history, the mother and father had hypertension, his father died due to ischemic stroke. On neurological examination, the patient's left side was hemiplegic, with no sitting balance. According to Brunnstrom stages, hand, upper extremity, and lower extremity were stage 1/1/1, respectively. The patient wore high pressure sockets to prevent lower extremity deep venous thrombosis. After 5 weeks of rehabilitation program, the patient was able to walk with a high-density ankle-foot orthosis and tripod. After a total of 45 days had passed since he came to the service, diffuse swelling was observed in hemiplegic lower extremity. A thrombus was detected in the vena saphena parva in Doppler ultrasound scanning. When venous thrombosis developed, our patient was not bedridden, he was able to walk with a high-density ankle-foot orthosis and tripod. The thrombophilia panel, level of fibrinogen and D-dimer were normal. The anticoagulant dose (enoxaparin 60 mg bid) was increased to 80 mg bid and rehabilitation program of the patient was suspended until the venous flow was observed in the lower extremity. A written informed consent was obtained from the patient.

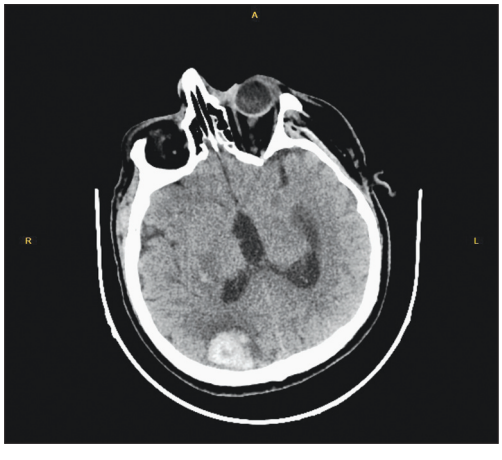

FIGURE 1: Brain computed tomography showed intracranial hematoma in the right parietal lobe as indicated with arrows.

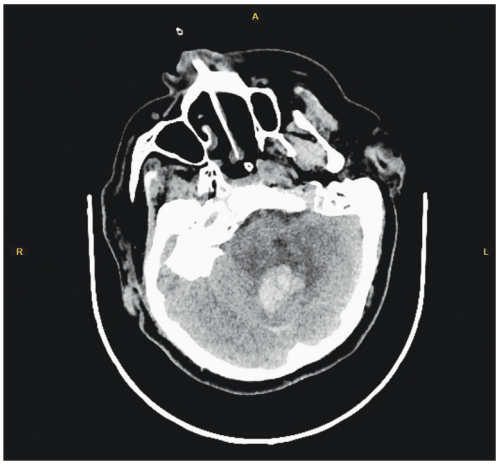

FIGURE 2: Brain computed tomography showed intracranial hematoma as indicated with arrows.

DISCUSSION

In this case, we showed the development of venous thrombosis in patients with COVID-19-related hemorrhagic stroke despite the use of anticoagulant ther-

apy and patient ambulation. This may be related to the thrombogenic effect of COVID-19. The association between COVID-19 and stroke has been shown in previous studies.[1-4] Ischemic stroke has been reported in most cases of COVID-19-related strokes in the literature. Mao et al. detected ischemic stroke in 6 patients and hemorrhagic stroke in only 1 patient in their study including 214 COVID-19 patients.[1] In the study of Li et al. including 219 COVID-19 patients, acute ischemic stroke was reported in 11 patients and hemorrhagic stroke in 1 patient.[4] It has been reported that stroke cases are more common in COVID-19 cases with moderate and severe clinical course compared to respiratory system involvement, and cases are seen in the early period of the disease.[1] In our case, the patient's COVID-19 infection was severe and he was intubated due to respiratory distress, hemorrhagic stroke was detected in the early period of the infection.

Hypertension and anticoagulant use are risk factors for intracranial hemorrhage. A case, in which Sharifi-Razavi et al. discussed the association between COVID-19 and ICH, did not have a history of hypertension or anticoagulant use.[3] Similarly, our patient did not have any disease or drug use in his history. A study done by Dogra et al. investigated the use of anticoagulants in patients positive for COVID-19 with ICH and found that most patients were given therapeutic doses of anticoagulant treatment prior to ICH discovery, and that a small number of patients were given both therapeutic anticoagulant and antiplatelet therapy.[11] Our patient was given therapeutic dose anticoagulant and antiplatelet therapy in the ICU before hemorrhagic stroke developed. Anticoagulant treatments used to prevent thrombotic complications may increase the risk of intracerebral bleeding. The risk of ICH should be kept in mind when deciding on the anticoagulant dose in COVID-19.

In studies investigating the incidence of the VTE of COVID-19, it was found that deep vein thrombosis developed in approximately 20-25% of COVID-19 patients treated in hospital, despite the use of prophylactic doses of anticoagulant agents.[12,13] Venous thrombosis has been reported even in COVID-19 patients treated with anticoagulation at therapeutic doses.[14] It has been reported in the literature that hypercoagulability related to COVID-19 may increase the risk of thromboembolic complications.[15] Immobilization and vascular damage have been added as other risk factors that increase the risk of thrombosis.[15] Beyrouti et al. detected cerebrovascular disease secondary to large vessel occlusion in 6 patients who were positive for COVID-19, and they detected simultaneous venous thrombosis in 2 of these cases.[5] A case of ischemic stroke has been reported in a COVID-19 patient despite consistent use of dual antiplatelet therapy before COVID-19.[16]

Wang et al. found that the risk of bleeding was high in 11% of the patients with high risk of VTE in COVID-19.[17] Therefore, they recommended that both the risk of VTE and the risk of bleeding should be evaluated regularly, the dose and duration of anticoagulants should be adjusted accordingly, and if necessary, elastic compression or intermittent pneumatic compression therapy should be added. Dogra et al. also reported that anticoagulation therapy may be considered in patients with COVID-19 despite the risk of ICH.[11]

In our case when venous thrombosis developed, the patient received a rehabilitation program and was able to walk. The thrombophilia panel, level of fibrinogen, and D-dimer were normal. Therefore we considered that thrombosis may have developed due to the thrombogenic effect of COVID-19.

In this paper, we analysed a trombogenic complication of the COVID 19 in a patient who was using anticoagulants. Since COVID-19 increases the risk of hypercoagulopathy and thrombosis, anticoagulant therapy may be considered in COVID-19-related hemorrhagic stroke. Depending on this process, regular follow-up of patients regarding VTE and bleeding risks is crucial to prevent undesirable events.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

REFERENCES

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683-90. [Crossref] [PubMed] [PMC]
2. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020;51:2002-11. Erratum in: Stroke. 2020;51:e179. [Crossref] [PubMed] [PMC]
3. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect. 2020;35:100669. [Crossref] [PubMed] [PMC]
4. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol. 2020;3:279-84. [Crossref] [PubMed] [PMC]
5. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020;91:889-91. [Crossref] [PubMed] [PMC]
6. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22. [Crossref] [PubMed] [PMC]
7. Md Noh MSF. COVID-19 and cerebral hemorrhage: proposed mechanisms. J Neuroradiol. 2021;48:125-6. [Crossref] [PubMed] [PMC]
8. Paciaroni M, Agnelli G, Alberti A, et al. PREvention of VENous thromboembolism in hemorrhagic stroke patients - PREVENTIHS study: a randomized controlled trial and a systematic review and meta-analysis. Eur Neurol. 2020;83:566-75. [Crossref] [PubMed]
9. Qian C, Huhtakangas J, Juvela S, et al. Early vs. late enoxaparin for the prevention of venous thromboembolism in patients with ICH: A double blind placebo controlled multicenter study. Clin Neurol Neurosurg. 2021;202:106534. [Crossref] [PubMed]
10. Cai Q, Zhang X, Chen H. Patients with venous thromboembolism after spontaneous intracerebral hemorrhage: a review. Thromb J. 2021;19:93. [Crossref] [PubMed] [PMC]
11. Dogra S, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis. 2020;29:104984. [Crossref] [PubMed] [PMC]
12. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1995-2002. [PubMed] [PMC]
13. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7. [Crossref]
14. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18:1743-6. [Crossref] [PubMed] [PMC]
15. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7:e438-e40. [Crossref] [PubMed] [PMC]
16. Mahboob S, Boppana SH, Rose NB, et al. Large vessel stroke and COVID-19: Case report and literature review. eNeurologicalSci. 2020;20:100250. [Crossref] [PubMed] [PMC]
17. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol. 2020;7:e362-e3. [Crossref] [PubMed] [PMC]