



Ruptured Cerebral Aneurysms and Dissecting Aneurysms in Patients with COVID-19: A Case Series and Literature Review

Daisuke Wajima^{1*} Rin Shimozato¹ Tomonori Takeshita¹ Tomoaki Nagamine¹

¹ Department of Neurosurgery, Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, Okinawa, Japan

Address for correspondence Daisuke Wajima, MD, PhD, Department of Neurosurgery, Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, Arakawa 118-1, Haeburu, Shimajiri, Okinawa 9011193, Japan (e-mail: d.wajima@gmail.com).

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with a hypercoagulable state and ischemic stroke. However, aneurysmal subarachnoid hemorrhage (SAH) due to SARS-CoV-2 infection is uncommon. Here, we report a case series of SAH caused by ruptured cerebral aneurysms or dissecting aneurysms (DAs) in patients with coronavirus disease 2019 (COVID-19) and discuss the potential relationships between them.

Case Description Four of the six patients had a history of COVID-19, ranging from 2 to 9 days, one had COVID-19 pneumonia for 1 month, and one had SARS-CoV-2 positivity on admission. Plain head computed tomography revealed diffuse SAH in all cases, while angiography revealed a DA in the right posterior cerebral artery (P2 portion) in patient 1, DA in the right vertebral artery (VA) in patients 2 and 6, anterior communicating artery aneurysm in patient 3, blister aneurysm in the right internal cerebral artery (ICA) (C2 portion) in patient 4, and DAs in the right VA and extracranial portion of the right ICA in patient 5. Treatment comprised internal trapping for patients 1, 2, and 6; neck clipping for patient 3; stent-assisted coiling for patient 4; and internal trapping and flow diversion for patient 5. All the patients' postoperative courses were uneventful.

Conclusion The present cases alone do not provide clear evidence on whether SARS-CoV-2 infection causes ruptured cerebral aneurysms or DAs. Therefore, accumulation of more cases and further studies are needed to clarify the relationship between SARS-CoV-2 infection and these aneurysm conditions.

Keywords

- angiography
- COVID-19
- intracranial aneurysms
- ischemic stroke
- SARS-CoV-2
- subarachnoid hemorrhage

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes a hypercoagulable state¹ and is associated with ischemic stroke.² Although aneurysmal subarachnoid hemorrhage (SAH) due to SARS-CoV-2 infection is uncommon,³ its clinical characteristics need to be investigated to identify potential serious neurological sequelae. Here, we report a case series of patients with coronavirus disease 2019

(COVID-19) who had SAH caused by ruptured cerebral aneurysms or dissecting aneurysms (DAs).

Case Description

Our hospital's treatment protocol for ruptured cerebral aneurysms is as follows. First, they are treated with neck clipping or Interventional Radiology (IVR) (coil embolization or flow-diverter replacement) to stabilize the patient's

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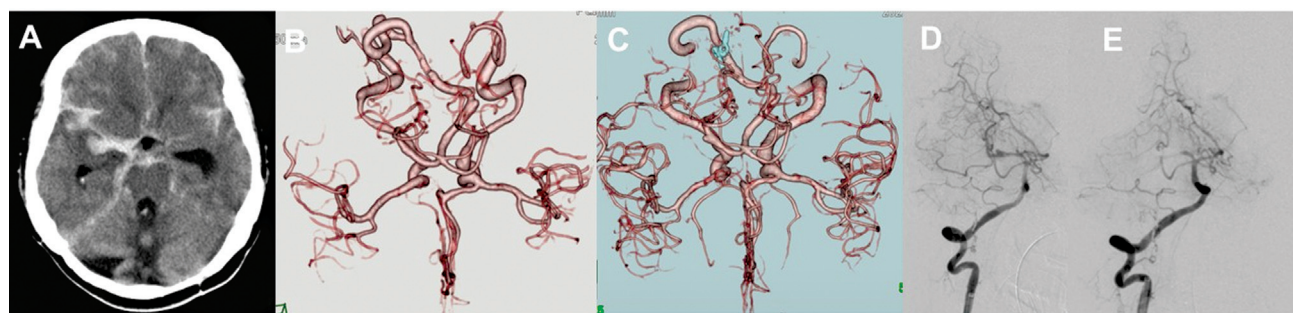


Fig. 1 Initial plain head computed tomography (CT) scan of patient 1. CT scan shows diffuse subarachnoid hemorrhage (SAH) (A), and three-dimensional CT angiography (3D-CTA) scan demonstrates no apparent aneurysmal changes other than the postoperative changes in the right vertebral artery dissecting aneurysm (B). Two weeks after SAH onset, rupture of the right posterior cerebral artery (PCA) dissecting aneurysm can be observed on the patient's head CT and 3D-CTA (C). Digital subtraction angiography scan shows a growing dissecting aneurysm in the right PCA (P2 portion). Ventricular drainage and internal trapping using coils were performed immediately (D, E).

general condition. Thereafter, spinal, cisternal, or ventricular drainage is performed to decrease the SAH.

Case 1

A 47-year-old woman was admitted to our emergency room after she was found unconscious in her room. She had had COVID-19 for 5 days. At age 32, she was treated for a ruptured right vertebral artery (VA)-DA, with no recurrence. Plain computed tomography (CT) revealed diffuse SAH (►Fig. 1A). Three-dimensional CT angiography (3D-CTA) revealed no aneurysmal changes other than the postoperative changes of the right VA-DA (►Fig. 1B). Two weeks later, head CT and 3D-CTA revealed a right posterior cerebral artery (PCA)-DA rupture (►Fig. 1C). Digital subtraction angiography (DSA) revealed a growing right PCA-DA (P2 portion). Ventricular drainage and internal trapping using coils were performed immediately (►Fig. 1D, E). Thereafter, the patient underwent shunt placement for hydrocephalus. She was transferred to a rehabilitation hospital and recovered (modified Rankin scale [mRS] score of 3 at 2 months).

Case 2

A 43-year-old man found in a convulsive state at home was transferred to our emergency room. He had had COVID-19 for 7 days. He had no obvious risk factors for atherosclerosis or DA.

Head CT revealed diffuse SAH (►Fig. 2A). 3D-CTA revealed a right VA-DA (►Fig. 2B). Internal trapping of the right VA-DA proximal to the posterior inferior cerebellar artery (PICA) was performed immediately using coils (►Fig. 2C, D). Two weeks later, stent-assisted coil embolization was performed for the residual DA (►Fig. 2E). The patient was discharged home and recovered (mRS score of 1 at the 1-month follow-up).

Case 3

A 52-year-old man with sudden-onset coma was transferred to our emergency room. He had had COVID-19 pneumonia for 1 month. Head CT revealed diffuse SAH (►Fig. 3A). 3D-CTA revealed an anterior communicating artery aneurysm (►Fig. 3B). Ventricular drainage and neck clipping were performed immediately (►Fig. 3C). This patient also underwent shunt placement for hydrocephalus occurring postoperatively. He underwent rehabilitation and recovered (mRS score of 4 at 2 months after coil embolization).

Case 4

A 37-year-old woman experienced sudden-onset headache. She had had COVID-19 for 1 day and had undergone kidney transplantation 2 days previously. Head CT revealed diffuse SAH (►Fig. 4A). DSA revealed a blister aneurysm at the C2 portion of the right internal cerebral artery (ICA) (►Fig. 4B).

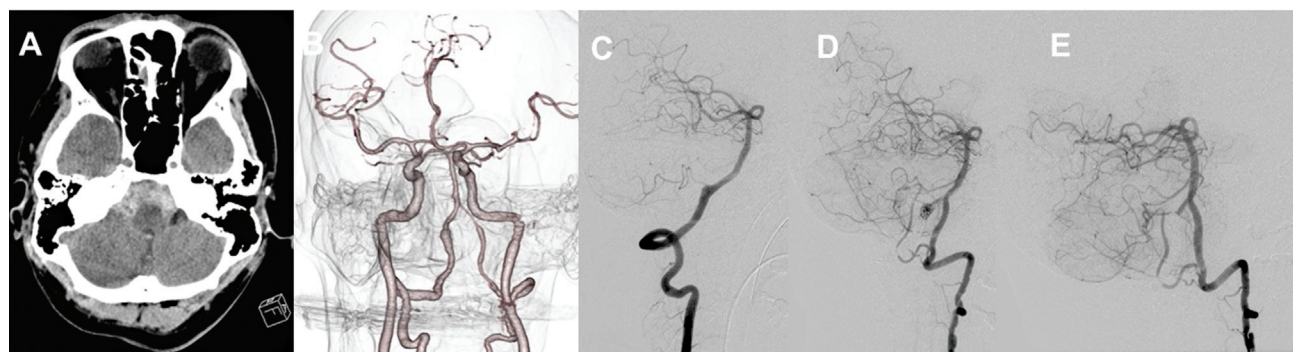


Fig. 2 Plain head computed tomography (CT) scan of patient 2. CT scan shows diffuse subarachnoid hemorrhage (SAH) (A), while three-dimensional CT angiography scan shows a right vertebral artery (VA) dissecting aneurysm (DA) (B). Internal trapping of the right VA-DA proximal to the posterior inferior cerebellar artery using coils was performed immediately (C, D). Two weeks after SAH onset, stent-assisted coil embolization was performed for the residual DA (E).

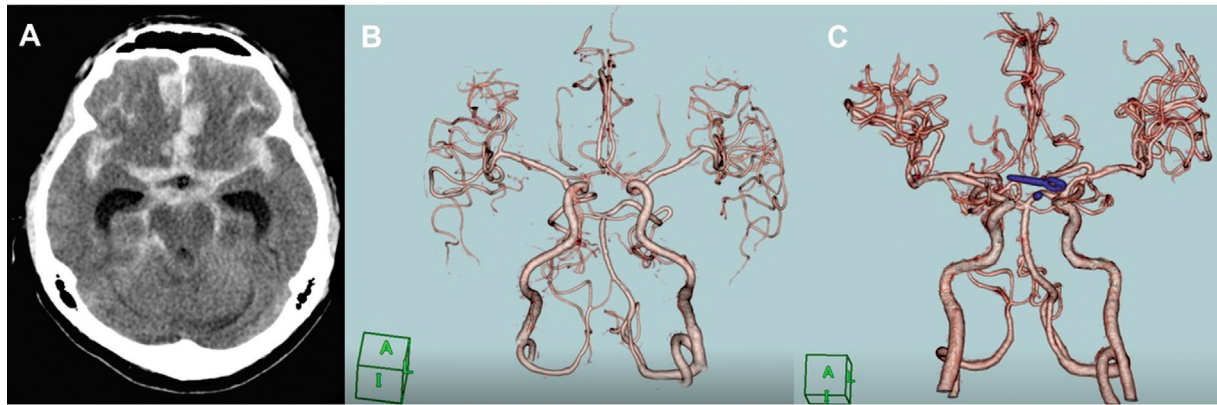


Fig. 3 Plain head computed tomography (CT) scan of patient 3. CT scan shows diffuse subarachnoid hemorrhage (A), and three-dimensional CT angiography scan shows an anterior communicating artery aneurysm (B). Ventricular drainage and neck clipping were performed immediately (C).

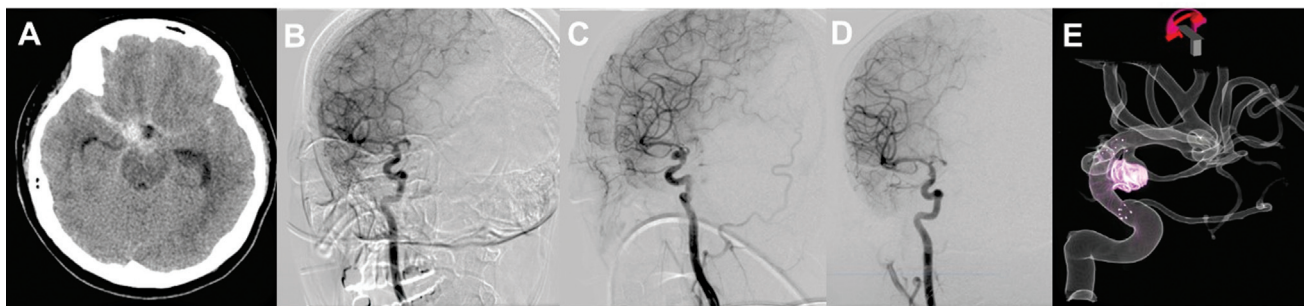


Fig. 4 Plain head computed tomography (CT) scan of patient 4. CT scan shows diffuse subarachnoid hemorrhage (SAH) (A), while digital subtraction angiography (DSA) scan demonstrates a blister aneurysm at the C2 portion of the right internal cerebral artery (B). Two weeks after SAH onset, the digital subtraction angiography scan reveals that the aneurysm is growing (C); subsequently, stent-assisted coil embolization and flow diverter stent placement were performed to treat the blister aneurysm (D, E).

Two weeks later, DSA revealed aneurysm growth (►Fig. 4C). Stent-assisted coil embolization and flow diverter stent placement were performed to treat the blister aneurysm (►Fig. 4D, E). She was discharged and recovered (mRS score of 1 at the 1-month follow-up).

Case 5

A 43-year-old man found in a convulsive state was admitted to our emergency room. He had had COVID-19 for 9 days and was receiving hypertension treatment. Head CT revealed diffuse SAH (►Fig. 5A). 3D-CTA indicated DAs in the right

VA and extracranial portion of the right ICA (►Fig. 5B). Internal trapping of the right VA-DA proximal to the PICA was performed immediately using coils (►Fig. 5C, D). One month later, he underwent flow diverter placement for the growing right ICA-DA (►Fig. 5E). He was discharged home and recovered (mRS score of 1 at the 2-month follow-up).

Case 6

A 37-year-old woman at 37 weeks of gestation was transferred to our emergency room owing to sudden consciousness disturbance. She was receiving hypertension

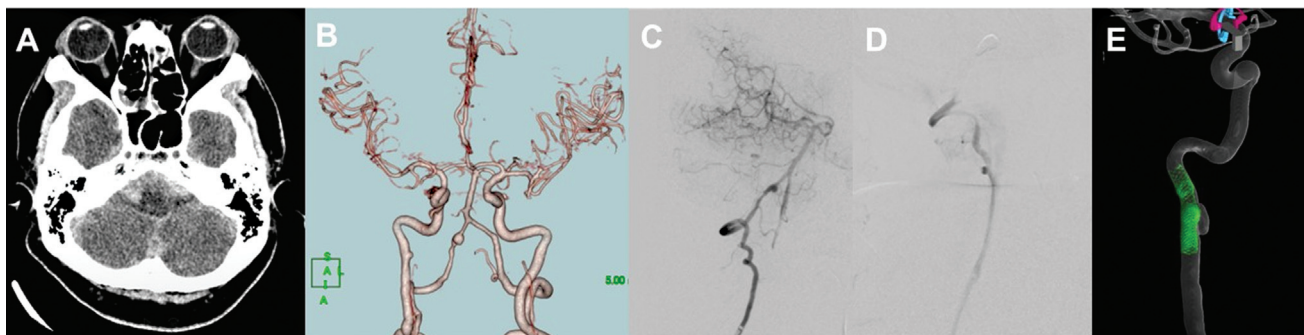


Fig. 5 Plain head computed tomography (CT) scan of patient 5. CT scan shows diffuse subarachnoid hemorrhage (SAH) (A), and three-dimensional CT angiography scan shows a right vertebral artery (VA) dissecting aneurysm (DA) and DA in the extracranial portion of the right internal cerebral artery (ICA) (B). Internal trapping of the right VA-DA proximal to the posterior inferior cerebellar artery using coils was performed immediately (C, D). One month after SAH onset, flow diverter placement was performed to treat the growing right ICA-DA (E).

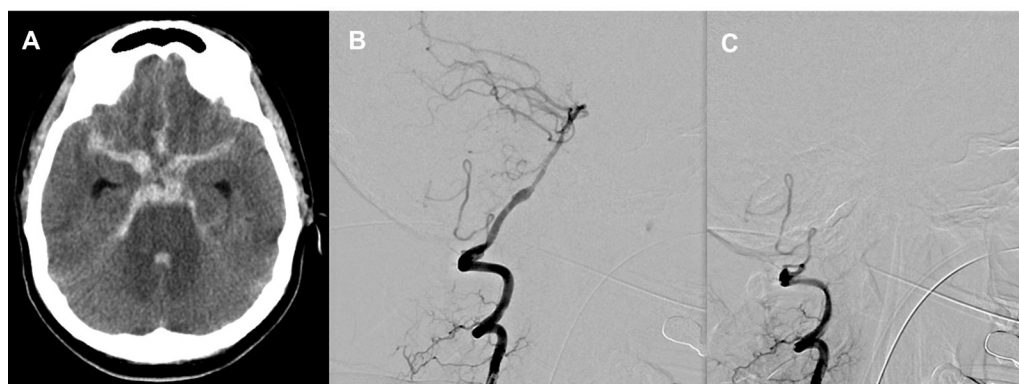


Fig. 6 Plain head computed tomography (CT) scan of patient 6. CT scan shows diffuse subarachnoid hemorrhage (A), while digital subtraction angiography scan demonstrates right vertebral artery (VA) dissecting aneurysm (DA) (B). Internal trapping of the right VA-DA proximal to the posterior inferior cerebellar artery using coils was performed immediately (C).

treatment. Head CT revealed diffuse SAH (►Fig. 6A). DSA revealed a right VA-DA (►Fig. 6B). Polymerase chain reaction testing at the time of hospitalization revealed SARS-CoV-2 positivity. Internal trapping of the right VA-DA proximal to the PICA was performed immediately using coils (►Fig. 6C), followed by a caesarean section. She was discharged home and recovered (mRS score of 1 at the 2-month follow-up).

Discussion

The impact of COVID-19 on SAH remains unclear; however, COVID-19 reportedly induces cerebral arterial aneurysm rupture and DAs.⁴ To date, 22 cases have been reported in six studies,^{5–9} including ours (►Table 1). In these cases, saccular aneurysms in the anterior circulation (ICA, middle cerebral artery, and anterior communicating artery) were found in 10 patients (45%), DAs, or blister aneurysms in the anterior circulation in six (27%), and DAs in the posterior circulation (the VA) in six (27%). Moreover, 8 of 12 patients (67%) with symptomatic COVID-19 had SAH, and 5 of 8 patients (63%) with symptomatic COVID-19 had ruptured DAs or blister aneurysms. Additionally, the rates of hypertension and smoking history were 43 (6 of 14 cases) and 17% (2 of 12 cases), respectively.

Although our report does not provide direct evidence linking ruptured cerebral aneurysms or DAs with COVID-19, less than half of the patients showed associations of hypertension and smoking history with cerebral aneurysms or DAs. Of our six patients, 83% had DAs or blister aneurysms and 80% had a history of symptomatic COVID-19. Moreover, SAH, especially that related to blister aneurysms and DAs, occurred within 2 to 9 days of COVID-19 onset.

In general, adults with SARS-CoV-2 infection can be grouped into the following categories according to illness severity (COVID-19 Treatment Guidelines [nih.gov]):

- *Asymptomatic/presymptomatic infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (a nucleic acid amplification test or an antigen test) but have no symptoms consistent with COVID-19.

- *Mild illness:* Individuals who have signs and symptoms of COVID-19 other than shortness of breath, dyspnea, and abnormal chest imaging.
- *Moderate illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured via pulse oximetry (SpO₂) more than or equal to 94% on room air at sea level.
- *Severe illness:* Individuals with an SpO₂ <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen less than 300 mm Hg, respiratory rate more than 30 breaths/min, or lung infiltrates more than 50%.
- *Critical illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

In our literature review (21 cases), three patients were asymptomatic and eight had mild illness (►Table 1). In our case series, all patients were asymptomatic or had mild illness.

The entry of SARS-CoV-2 into the human body is dependent on angiotensin-converting enzyme 2 (ACE2) receptors.¹⁰ Besides ACE2, three other mediators for viral entry into cells have been suggested, including extracellular matrix metalloproteinase inducer (CD147), sialic acid, and transmembrane serine protease 2, which are found in endothelial and arterial smooth muscle cells.¹⁰ SARS-CoV-2 can destroy the endothelium of blood vessels and cause endothelial dysfunction. Inflammatory cytokines released by lymphocytes and macrophages, such as interleukin (IL)-1 β and tumor necrosis factor- α (TNF- α), can also cause endothelial dysfunction.¹⁰ These dysfunctional mechanisms cause imbalances that can cause vasoconstriction and lead to vascular damage, ultimately inducing brain hemorrhage.¹⁰

Furthermore, patients with SARS-CoV-2 positivity reportedly have an increased systemic inflammation due to an imbalance in the T helper cell population caused by an exaggerated Th1 response.¹⁰ Similar alterations in T helper cell populations have been observed in patients with intracranial aneurysms.¹¹ COVID-19 reportedly induces cytokine storms, increasing IL-1, IL-6, IL-8, IL-18, and TNF-

Table 1 Characteristics and clinical features of patients with ruptured cerebral aneurysms or dissecting aneurysms complicated with COVID-19

Case	Age (y)	Sex	Aneurysm location	Aneurysm morphology	Aneurysm size (mm)	Time from COVID-19 onset to SAH onset (days)	SARS-CoV-2 infection severity	Hypertension	Smoking history	Treatment
Sato et al ⁴	58	Female	Rt VA	Dissectional aneurysm	N/A	10	Mild illness	No	No	Internal trapping by endovascular coiling
Dodd et al ⁷	N/A	N/A	A-com A	aneurysm	3	N/A	N/A	N/A	N/A	Coiling
	N/A	N/A	A-com A	aneurysm	3	N/A	N/A	N/A	N/A	Coiling
	N/A	N/A	Lt MCA	aneurysm	4	N/A	N/A	N/A	N/A	Clipping
	N/A	N/A	Achor A	aneurysm	1.5	N/A	N/A	N/A	N/A	Flow diversion
	N/A	N/A	P-com A	aneurysm	15	N/A	N/A	N/A	N/A	Clipping
	N/A	N/A	Lt Oph-A	aneurysm	19	N/A	N/A	N/A	N/A	Coiling
	N/A	N/A	Rt VA	Dissectional aneurysm	5	N/A	N/A	N/A	N/A	Flow diversion
Fiani et al ¹¹	N/A	N/A	PICA	Dissectional aneurysm	5	N/A	N/A	N/A	N/A	Flow diversion
	N/A	N/A	A-com A	Dissectional aneurysm	15	N/A	N/A	N/A	N/A	Coiling
	N/A	N/A	PCA	Dissectional aneurysm	21	N/A	N/A	N/A	N/A	Patient expired prior to treatment
	52	Male	Lt P-com A	aneurysm	6	High fever (SARS-CoV-2 PCR-positive on admission)	Mild illness	Yes	N/A	Coiling
	61	Male	A-com A	aneurysm	N/A	14	Mild illness	Yes	No	Coiling
	70	Male	Rt MCA	aneurysm	N/A	Asymptomatic (SARS-CoV-2 PCR-positive on admission)	Asymptomatic	No	N/A	Clipping
	13	Female	Lt MCA	Dissectional aneurysm	8	Asymptomatic (SARS-CoV-2 PCR-positive on admission)	Asymptomatic	No	No	Trapping by clipping
Case 4	37	Female	Rt ICA	aneurysm	8.5	2	Mild illness	No	No	Stent-assisted coiling
Case 5	50	Male	Rt VA	Dissectional aneurysm	4.5	9	Mild illness	Yes	No	Internal trapping by endovascular coiling
			Rt ICA	Dissectional aneurysm	7.4					Flow diversion

(Continued)

Table 1 (Continued)

Case	Age (y)	Sex	Aneurysm location	Aneurysm morphology	Aneurysm size (mm)	Time from COVID-19 onset to SAH onset (days)	SARS-CoV-2 infection severity	Hypertension	Smoking history	Treatment
Case 1	48	Female	Rt PCA P2	Dissectional aneurysm	3.5	5	Mild illness	No	No	Internal trapping by endovascular coiling
Case 2	44	Male	Rt VA	Dissectional aneurysm	6	7	Mild illness	Yes	Yes	Internal trapping by endovascular coiling
Case 3	53	Male	A-com A	aneurysm	4.1	30	Mild illness	Yes	Yes	Clipping
Case 6	37	Female	Rt VA	Dissectional aneurysm	3.7	Asymptomatic (SARS-CoV-2 PCR-positive on admission)	Asymptomatic	Yes	No	Internal trapping by endovascular coiling

Abbreviations: Achor A, anterior choroidal artery; A-com A, anterior communicating artery; COVID-19, coronavirus disease 2019; ICA, internal cerebral artery; Lt, left; MCA, middle cerebral artery; N/A, not available; Oph-A, ophthalmic artery; PCA, posterior cerebral artery; P-com A, posterior communicating artery; PCR, polymerase chain reaction; PCA, posterior inferior cerebellar artery; Rt, right; SAH, subarachnoid hemorrhage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VA, vertebral artery.

α production.¹² Thus, the systemic immune-inflammation index is considered a potent marker of severe clinical outcomes in patients with COVID-19. Systemic inflammation causes vascular injury, resulting in collagen breakdown and increased blood–brain barrier permeability. High levels of these inflammatory cytokines may increase the risk of intracranial aneurysms and SAH.¹³ High IL-6 levels have been linked to poor outcomes after aneurysmal rupture and in patients with COVID-19.^{14,15}

The risk of posterior circulation ischemic stroke is high after an average of 5 days of symptomatic COVID-19, possibly due to COVID-19-induced hyper-inflammation and vascular injury.¹³ Additionally, DAs in small arteries may develop because of COVID-19-induced hyper-inflammation causing a tear in the intima and internal elastic lamina.^{13,16} DAs may develop in the main trunk arteries because of COVID-19-induced inflammatory obstruction of the capillaries from the vasa vasorum, causing degeneration of the tunica media.^{13,16} Therefore, recovery from COVID-19 may take a long time. Furthermore, local inflammation of the arterial wall caused by systemic inflammation may involve the formation of fragile DAs.¹⁶ Moreover, COVID-19-triggered inflammatory responses and endothelial dysfunction may rupture atherosclerotic plaques, leading to the formation of hematomas in the arterial walls and DAs.¹³ However, as histological examination was not performed in our study, we have no evidence of whether COVID-19-induced inflammatory obstruction of the capillaries from the vasa vasorum or arterial wall inflammation occurred. Pathological studies are needed to clarify the relationship between COVID-19 and ruptured cerebral aneurysms or DAs.

Conclusion

We reported a case series of six patients, reviewed previous cases of ruptured cerebral aneurysms or DAs associated with COVID-19, and discussed their potential relationships. More research is needed to explore these relationships.

Ethics Statement and Informed Consent

This study complies with all relevant national regulations and institutional policies and the tenets of the Helsinki Declaration. It has been approved by the institutional review board or equivalent committee of the institution to which the authors are affiliated. Written informed consent was provided by all patients in this study.

Conflict of Interest

None declared.

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