



Case Report

Nonaneurysmal subarachnoid hemorrhage associated with COVID-19 infection: A case report

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ABSTRACT

Background: Most coronavirus disease 2019 (COVID-19)-related cerebrovascular disorders are ischemic while hemorrhagic disorders are rarely reported. Among these, subarachnoid hemorrhage (SAH) is very rarely reported and nonaneurysmal SAH has been reported in only about a dozen cases. Here, we report a case of nonaneurysmal SAH as the only clinical manifestation of COVID-19 infection. In addition, we reviewed and analyzed the literature data on cases of nonaneurysmal SAH caused by COVID-19 infection.

Case Description: A 50-year-old woman presented to an emergency department with a sudden headache, right hemiparesis, and consciousness disturbance. At that time, no fever or respiratory failure was observed. Laboratory data were within normal values but the rapid antigen test for COVID-19 on admission was positive, resulting in a diagnosis of COVID-19 infection. Computed tomograms (CTs) showed bilateral convexal SAH with a hematoma but three-dimensional CT angiograms showed no obvious sources, such as a cerebral aneurysm. Therefore, the patient was diagnosed with nonaneurysmal SAH associated with COVID-19 infection. With conservative treatment, consciousness level and hemiparesis both improved gradually until transfer for continued rehabilitation. Approximately 12 weeks after onset, the patient was discharged with only mild cognitive impairment. During the entire course of the disease, the headache, hemiparesis, and mild cognitive impairment due to nonaneurysmal SAH with small hematoma were the only abnormalities experienced.

Conclusion: Since COVID-19 infection can cause nonaneurysmal hemorrhaging, it should be considered (even in the absence of characteristic infectious or respiratory symptoms of COVID-19) when atypical hemorrhage distribution is seen as in our case.

Keywords: Coronavirus disease 2019, Nonaneurysmal subarachnoid hemorrhage, Stroke

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 infection can affect the respiratory tract and other organs, including the brain, and is considered a risk factor for multiorgan ischemic and hemorrhagic diseases.^[18] For example, it has been reported that approximately 0.7–1.4% of COVID-19 infections result in a stroke.^[18] It is also known to cause coagulation abnormalities and ischemic strokes are more common than hemorrhagic strokes. In addition, COVID-19-

related strokes tend to develop in younger patients with more severe manifestations than strokes in uninfected patients.^[19]

A higher incidence of aneurysmal subarachnoid hemorrhage (SAH) has been reported in COVID-19 patients, but whether this increase is incidental or related is controversial.^[3,4] In addition, there are few reports on the association between COVID-19 and nonaneurysmal SAH, especially regarding clinical features still poorly understood.

Here, we describe a case of nonaneurysmal SAH with small hematoma, resulting in headache, hemiparesis, and mild cognitive impairment as the only abnormalities related to COVID-19 infection. We also review previously reported cases of nonaneurysmal SAH associated with COVID-19 infection and discuss their characteristics.

CASE DESCRIPTION

A 50-year-old woman came to our emergency department complaining of a sudden headache, right hemiparesis, and loss of consciousness. She had no significant or relevant medical history other than a previous, small, and unruptured cerebral aneurysm for which she had undergone regular imaging.

On admission, physical examination revealed a body temperature of 98.2°F, respiratory rate of 20 breaths/min, peripheral oxygen saturation of 98% on room air, and blood pressure of 147/86 mmHg. The right hemiparesis with the upper extremity predominance and mild consciousness disturbance was observed. General laboratory findings, including thyroid function and factors associated with collagen diseases, were within normal ranges, and there were no inflammatory findings or coagulation abnormalities (PT: 11.1 s, APTT: 28.7 s, and D-dimer: 0.7 µg/dl). Our institution performs antigen testing in all patients who require hospitalization to prevent nosocomial infection; this patient tested positive by the rapid antigen test and was diagnosed with COVID-19. The chest X-ray was normal, and the chest computed tomogram (CT) showed no pneumonia. CT of the brain showed SAH over a wide area of the bilateral convexal regions and a hematoma in the left frontal sulci [Figure 1]. A three-dimensional CT angiogram showed no vascular lesions that could be an obvious hemorrhage source. An aneurysm of the left internal carotid artery was identified, which had been previously indicated, but it appeared to be unruptured based on the SAH distribution [Figure 2a].

Although no respiratory symptoms were present, remdesivir was administered for the viral infection, as SAH is a likely indicator of severe COVID-19. In addition, conservative treatment, including hemostatic agent administration, osmotic therapy, blood pressure control, and continuous rehabilitation, gradually improved neurological deficits such as consciousness disturbance and hemiparesis. Magnetic resonance (MR)

angiograms and contrast-enhanced MR images 14 days after admission showed no vascular or neoplastic lesions suggestive of a hemorrhage source. Approximately 12 weeks after onset, the patient was discharged with only mild cognitive impairment. During hospitalization, the patient had no respiratory symptoms or recurrent hemorrhagic/ischemic strokes. No hemorrhage sources were seen on MR images at the time of discharge [Figure 2b].

DISCUSSION

SAH is primarily caused by trauma or ruptured cerebral aneurysms but other causes include rupture of abnormal vessels (such as arteriovenous malformations and arteriovenous fistulas), vasculitis, tumors, arterial dissection, moyamoya disease, coagulation abnormalities, cocaine abuse, sickle cell disease, infection, perimesencephalic nonaneurysmal SAH, cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, cerebral amyloid angiopathy, and others.^[13,14,20] Regardless of cause, SAH is a severe disease with a poor prognosis, requiring case- and cause-specific treatment. Therefore, it is essential to promptly identify the cause of hemorrhaging. In our case, COVID-19 infection appeared to have caused nonaneurysmal SAH. Although the presence of a nonvisualized small aneurysm or dissection in the left frontal hematoma could not be ruled out, no clear source of bleeding was identified on MR imaging (including MR angiography) at admission, 14 days after admission, or at discharge.

A literature review revealed 16 cases of nonaneurysmal SAH associated with COVID-19 infection, including ours [Table 1].^[1-4,6,7,9,12,16,17,23,24] The average age of onset for nonaneurysmal SAH associated with COVID-19 infection was 57 years, similar to SAH due to cerebral aneurysm rupture. There was no gender difference in COVID-19-associated nonaneurysmal SAH, while SAH due to cerebral aneurysm rupture seems to be more common in women.

Among these cases, preceding neurological symptoms were extant in 5 cases (31.3%) and respiratory symptoms were

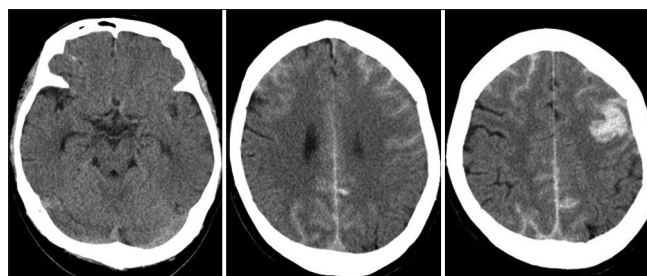


Figure 1: Computed tomograms on admission showing bilateral subarachnoid hemorrhage (SAH) with a hematoma in the left frontal sulci (middle and right). No SAH is seen in the basal cistern (left).

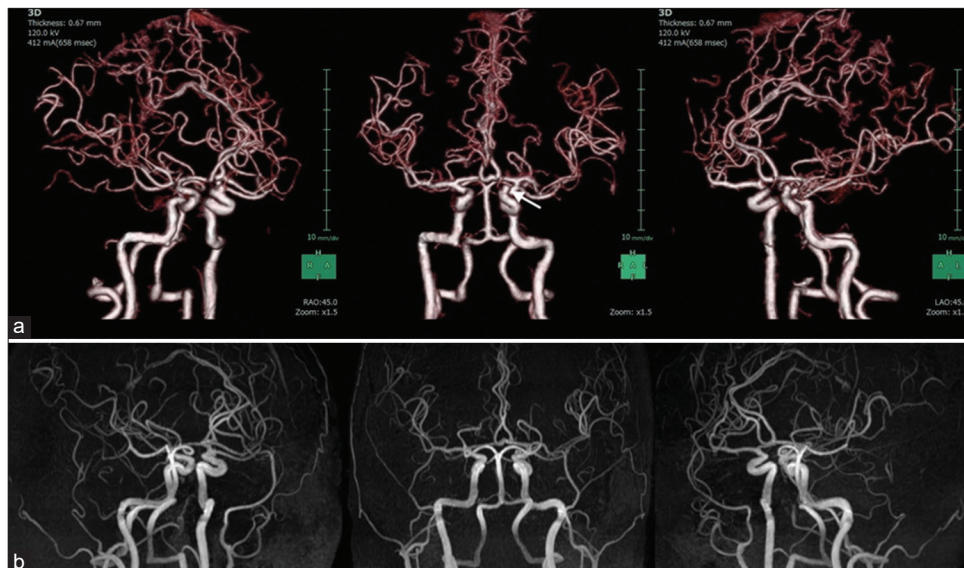


Figure 2: (a) Three-dimensional computed tomographic angiograms showing no clear source of hemorrhage. A small aneurysm arising from the left internal carotid artery (arrow) appears to be unruptured. (b) Magnetic resonance angiograms at discharge showing no clear source of hemorrhage.

seen in 11 cases (68.8%), indicating the challenge of precise COVID-19 infection diagnosis based on chief complaints in about 1/3 of the cases. Of the total cases, eight exhibited severe respiratory failure requiring ventilation but, even with preceding neurological symptoms, severe respiratory failure was later observed in 3 out of 5 patients (60.0%). Therefore, COVID-19 infection respiratory status requires continuous monitoring even if no initial abnormalities are observed.

Some cases presented stroke-specific symptoms, such as consciousness disturbance and hemiplegia, while others had only nonspecific symptoms such as headache. Headache is a common symptom of infectious diseases but the possibility of nonaneurysmal SAH should always be considered. As reported intervals from infection to nonaneurysmal SAH onset ranged from 0 to 30 days (average of 7.8 ± 9.4 days), COVID-19 patients could develop SAH at approximately 2 weeks after infection.

In addition, SAH distribution patterns in COVID-19 patients often differed from those caused by ruptured cerebral aneurysms. Ruptured cerebral aneurysm patterns for SAH vary depending on location but they generally spread in the basal cistern. In contrast, COVID-19 patients have a more peripheral hemorrhage distribution in the cortical areas. Several hemorrhagic mechanisms focused on vascular endothelial damage have been postulated for the etiology of SAH in COVID-19, including vascular barrier damage associated with hypercytokinemia, virus-induced endothelial damage, coagulopathy, and immune thrombocytopenia.^[5,8,28] In addition, small peripheral arteries are more susceptible to vascular injury than the thick-walled main arteries of the

brain, which may explain why SAH caused by COVID-19 infection is more common in cortical areas.

Some COVID-19 patients also had multiple cerebral infarctions.^[4,7,17] In ruptured cerebral aneurysms, cerebral infarction due to vasospasm may be seen which tends to coincide with the perfusion area of the spasmed vessel. In contrast, as seen in embolisms, COVID-19 patients tended to have multiple occurrences that did not coincide with the perfusion area of a single vessel.

Of the 13 patients with known prognoses, 5 (38.5%) had a favorable outcome, while 3 (23.1%) were severe disability and 5 (38.5%) died. The high mortality rate compared to typical COVID-19 infection (8.3~10%)^[11,22] was probably due to cumulative CNS damage caused by SAH and systemic damage caused by COVID-19 infection. Although such damage most likely indicates severe COVID-19, favorable outcomes may be obtained, even in the presence of SAH, as in our case. Therefore, appropriate treatment of both systemic infection and SAH-induced brain damage is necessary for a good prognosis while a prompt diagnosis of COVID-19 infection is essential.

Numerous reports of viral infections and nonaneurysmal SAH have been associated with COVID-19 caused by SARS-CoV-2,^[1-4,6,7,9,12,16,17,23,24] while some have been associated with other viruses including human immunodeficiency virus, herpes simplex virus, Epstein-Barr virus, Jamestown Canyon virus, and varicella zoster virus.^[10,15,21,25-27] Interestingly, there have been no reports of nonaneurysmal SAH caused by coronaviruses other than SARS-CoV-2, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1 or simply SARS-CoV) and Middle East respiratory syndrome

Table 1: Summary of the cases with nonaneurysmal SAH associated with COVID-19 infection.

Case No.	Author/year	Age/sex	Reason for admission	Neurological symptoms	Onset to SAH (day)	SAH distribution	Respiratory symptoms	Outcome
1	Cezar-Junior et al., 2020	53/M	Respiratory	Consciousness disturbance	4	Basal	Respiratory failure	MD
2		71/F	Respiratory	Headache, hemiparesis	7	Basal	Respiratory failure	SD
3	Haider et al., 2020	56/M	Respiratory	Consciousness disturbance	22	Convexal	Respiratory failure	n.d.
4	Harrogate et al., 2021	74/M	Respiratory	Consciousness disturbance	11	Convexal	Respiratory failure	MD
5		53/M	Respiratory	Seizure	n.d.	Convexal	Respiratory failure	MD
6	Basirjafari et al., 2021	9/M	Respiratory	Respiratory failure	1	Basal	respiratory failure	D
7	Batcik et al., 2021	36/F	Neurological	Respiratory failure	0	n.d. (Fisher 4)	Respiratory failure	n.d.
8	Mishra et al., 2021	79/F	Neurological	n.d.	n.d.	Convexal	Respiratory failure	D
9		83/F	Simultaneous	n.d.	n.d.	Convexal	Respiratory failure	D
10	Kvernland et al., 2021	60/n.d.	Respiratory	n.d.	15	Convexal	n.d.	SD
11	De Castillo et al., 2021	64/M	Neurological	Hemiparesis	0	Convexal	Pneumonia	SD
12	Mercado and Diaz, 2021	75/F	Neurological	Consciousness disturbance	0	Convexal	ARDS	D
13	Sarpoolaki et al., 2021	63/F	Respiratory	Headache	7	Basal	Cough, fever	n.d.
14	Ghosh et al., 2022	35/F	Respiratory	Headache	5	Basal	Fever	GR
15	Scheer et al., 2022	56/M	Respiratory	Consciousness disturbance	30	Convexal	n.d.	D
16	Present case, 2022	50/F	Neurological	Headache, hemiparesis	0	Convexal	(-)	GR

M: Male, F: Female, ARDS: Adult respiratory distress syndrome, n.d.: Not described, GOS: Glasgow Outcome Scale, GR: Good recovery, MD: Moderate disability, SD: Severe disability, D: Dead, SAH: Subarachnoid hemorrhage

coronavirus. As such, the true affinity of SARS-CoV-2 with cerebral vessels remains unknown in spite of an increasing number of reported cases. Further epidemiological and clinical studies are needed to clarify the relationship between COVID-19 infection and nonaneurysmal SAH and to find appropriate treatment.

CONCLUSION

In this report, we described a case of COVID-19 infection where nonaneurysmal SAH was an isolated symptom. There are two important lessons to be learned from this case. First, COVID-19 infection can cause nonaneurysmal SAH, which often has atypical hematoma distribution. Second, COVID-19 infection should be suspected in patients with atypical SAH distribution, even without typical infectious signs (such as fever or respiratory symptoms).

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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