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Aneurysmal Subarachnoid Hemorrhage in Patients with Coronavirus Disease 2019 (COVID-19): A Case Series

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■ **OBJECTIVE:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a pressing public health issue. Although most cases do not result in severe illness requiring hospitalization, there is increasing evidence that SARS-CoV-2–induced inflammation can exacerbate pre-existing diseases. We sought to describe the characteristics of patients with aneurysmal subarachnoid hemorrhage who were actively or very recently infected with SARS-CoV-2.

■ **METHODS:** We reviewed subarachnoid hemorrhage cases of patients who also were positive for SARS-CoV-2 at 5 high-volume cerebrovascular centers in the United States from March 2020 to January 2021. Cases of aneurysmal subarachnoid hemorrhage were analyzed.

■ **RESULTS:** A total of 10 patients were identified, consisting of 5 women (50%) and 5 men (50%). Median age was 38.5 years. Four of the 10 patients (40%) were asymptomatic with respect to SARS-CoV-2–related symptoms, 3 patients (30%) had mild-to-moderate symptoms, and 3 patients (30%) had severe coronavirus disease 2019 (COVID-19), with pneumonia and sepsis. Of the 10 cases, 4 had dissecting pseudoaneurysms (40%), 3 in the posterior circulation and 1 in the anterior circulation. Among 6 saccular/blister aneurysms, 4 (67%) were ≤4 mm in largest diameter.

■ **CONCLUSIONS:** Our experience with aneurysmal subarachnoid hemorrhage in patients positive for COVID-19

reveals a possibly distinct pattern compared with traditional aneurysmal subarachnoid hemorrhage, namely a high frequency of small aneurysms, dissecting pseudoaneurysms, and young patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named due to its ~80% genetic similarity with the original SARS coronavirus,¹ is a novel betacoronavirus that initiated the coronavirus disease 2019 (COVID-19) pandemic. Like other coronaviruses, SARS-CoV-2 has been shown to be able to invade the central nervous system via various routes, possesses neurotropism, and is neurovirulent.² There have been more than 175 million SARS-CoV-2/COVID-19 infections to date,³ with outcomes ranging from asymptomatic infection to multiorgan failure and death. The spectrum of disease severity following SARS-CoV-2 infection is a function of host immune response. Ineffective immune response can lead to exacerbated stimulation of innate immune cells, maladaptive inflammation, and development of the so-called “cytokine storm.”⁴ What remains unclear, however, is the full extent to which SARS-CoV-2 infection affects extrathoracic organs and the interactions between COVID-19–induced inflammation and preexisting comorbidities. Central nervous system complications have been reported in as many as 38% of patients with varying degrees of severity.⁵ There are accumulating reports of increased cerebrovascular injury⁶ and

Key words

- Cerebral aneurysm
- COVID-19
- SARS-CoV-2
- Stroke
- Subarachnoid hemorrhage

Abbreviations and Acronyms

(a)SAH: (Aneurysmal) subarachnoid hemorrhage

COVID-19: Coronavirus disease 2019

mRS: modified Rankin Scale

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

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ischemic stroke⁷ in patients with COVID-19, but reports on subarachnoid hemorrhage (SAH) and cerebral aneurysm rupture are limited to few case reports with largely nonaneurysmal SAH, and only 1 reported aneurysmal subarachnoid hemorrhage (aSAH) to date.⁸

The prevalence of cerebral aneurysms in the adult population is estimated to be between 2% and 4%.^{9,10} Most cerebral aneurysms are saccular in morphology, whereas fusiform, blister, and dissecting pseudoaneurysms are rare.^{11–13} The risk of an aneurysm rupturing is heavily influenced by risk factors like age, sex, smoking status, hypertension, and aneurysm size, morphology, and location, varying from 0% to 50% risk of rupture over a 5-year interval.^{13–15} Mechanistically, aneurysm formation is driven by weakening of the vascular internal elastic lamina secondary to hemodynamic stress and inflammation.¹⁶ Progressive inflammation, mediated predominantly by monocytes/macrophages,^{17,18} can then cause vascular smooth muscle cell apoptosis and vessel wall thinning, leading to aneurysm rupture and SAH.^{19,20}

We are observing across several institutions instances of aneurysm ruptures occurring in patients testing positive for COVID-19. The purpose of this study is to describe and analyze the characteristics of these patients.

METHODS

Patient Data

Data were collected retrospectively from patients treated at 5 high-volume cerebrovascular centers from March 2020 to January 2021 with a diagnosis of spontaneous SAH. Patients with a confirmed aneurysmal rupture and a diagnosis of SARS-CoV-2 infection (made based on reverse transcriptase-quantitative polymerase chain reaction testing of a nasopharyngeal swab sample from each patient during hospital admission and up to 28 days before admission following standard protocols^{21,22}) were included in the final analysis. The following data were collected from each patient's record: age, sex, aneurysm type, aneurysm location, Hunt and Hess classification, presenting symptoms, COVID-19 symptoms, aneurysm treatment, length of stay, modified Rankin scale (mRS) at discharge, history of hypertension, history of diabetes, history of cerebral aneurysms, history of chronic heart disease, and history of chronic lung disease. To preserve patient anonymity and in compliance with institutional review board regulations, we do not present the full data for individual cases and instead report the aggregated data or individual deidentified data points.

RESULTS

Patient Characteristics and Presentation

There were 10 patients. Patient characteristics are summarized in **Table 1**. There were 5 women (50%) and 5 men (50%). The median age was 38.5 years old (interquartile range: 36.5–45 years, range: 29–57 years). All 10 patients tested positive for COVID-19 when the SAH occurred. Four of the 10 patients (40%) were asymptomatic with respect to COVID-19–related symptoms, testing positive for the virus upon admission for aSAH. Three patients (30%) had mild-to-moderate symptoms, including cough, sore throat, and/or low-grade fever. The remaining 3 patients (30%)

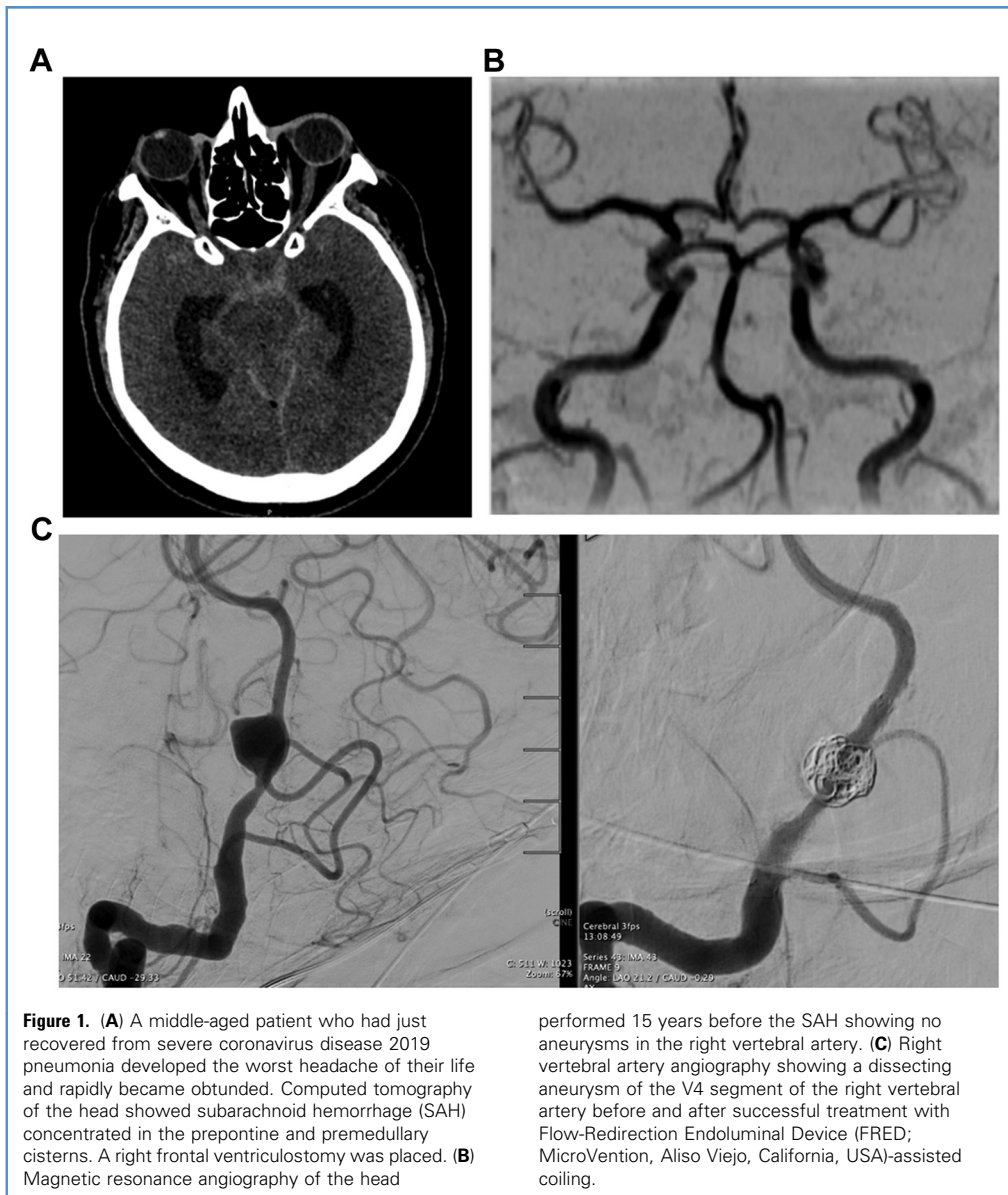
Table 1. Patient Characteristics and Presentation

Characteristic	N	%
Sex		
Female	5	50
Male	5	50
Age, years		
<30	1	10
30–40	5	50
40–50	2	20
>50	2	20
COVID-19 severity		
Asymptomatic	4	40
Mild	2	20
Moderate	1	10
Severe	3	30
Comorbidities		
Chronic lung disease	0	0
Chronic heart disease	0	0
Hypertension	1	10
Diabetes	0	0
Hunt and Hess grade		
1	0	0
2	3	30
3	3	30
4	3	30
5	1	10
Outcome		
Good recovery (mRS 0–2)	7	70
Moderate Disability (mRS 3–4)	1	10
Severe disability or death (mRS 5–6)	2	20

COVID-19, coronavirus disease 2019; mRS, modified Rankin Scale score.

had severe cases; all 3 were diagnosed with pneumonia and sepsis, and 1 patient also suffered acute kidney injury. One patient had recovered from COVID-19 pneumonia and sepsis before developing aSAH 2 weeks later. The patient was still positive for COVID-19 at the time of the hemorrhage. No patient had a documented history of chronic lung disease or chronic heart disease. Interestingly, 1 patient with a dissecting pseudoaneurysm of the right vertebral artery had a magnetic resonance imaging study of the brain from 2005 that showed no evidence of aneurysm at that time (**Figure 1**).

Hunt and Hess grades were as follows: grade II, 3 patients (30%); grade III, 3 patients (30%); grade IV, 3 patients (30%); grade V, 1 patient (10%) (**Table 1**).



Aneurysm Features and Treatment

Of the 10 cases reviewed, there were 5 saccular aneurysms (50%), 1 blister-type aneurysm (10%), and 4 dissecting pseudoaneurysms (40%). Of note, one patient died before we obtained a cerebral angiogram, but imaging was highly suspicious for a dissecting pseudoaneurysm of the left posterior cerebral artery. The saccular aneurysms were 3, 3, 4, 15, and 19 mm in diameter whereas the blister aneurysm was only 1.5 mm. The dissecting pseudoaneurysms were 5, 6, 15, and 21 mm in diameter.

Aneurysm location, type, and treatment are summarized in **Table 2**. Seven aneurysms (70%) occurred in the anterior circulation (3 in the anterior communicating artery, 1 in the middle cerebral artery, 1 in the posterior communicating segment, 1 in the ophthalmic segment, and 1 anterior choroidal

aneurysm) and 3 (30%) occurred in the vertebrobasilar system (all 3 were dissecting pseudoaneurysms; 1 in the posterior cerebral artery, 1 in the posterior inferior cerebellar artery (**Figure 2**), and 1 in the vertebral artery). Three aneurysms were treated with endovascular coiling (**Figure 3**), 3 with microsurgical clipping, and 3 with flow diversion. One patient who presented with a poor neurologic examination and did not improve after a decompressive hemicraniectomy died without undergoing aneurysm treatment.

Patient Outcomes

One patient developed cerebral vasospasm and delayed cerebral ischemia and underwent infusion of intra-arterial verapamil. Another patient underwent evacuation of a postoperative

Table 2. Aneurysm Features and Treatment

Case	Aneurysm Location	Aneurysm Morphology	Aneurysm Size, mm	Treatment
1	Anterior communicating artery	Saccular	3	Coiling
2	Anterior communicating artery	Saccular	3	Coiling
3	Left middle cerebral artery	Saccular	4	Clipping
4	Anterior choroidal artery	Blister	1.5	Flow diversion
5	Posterior communicating artery	Saccular	15	Clipping
6	Left ophthalmic artery	Saccular	19	Coiling
7	Right vertebral artery	Dissecting pseudoaneurysm	5	Flow diversion
8	Posterior inferior cerebellar artery	Dissecting pseudoaneurysm	5	Flow diversion
9	Anterior communicating artery	Dissecting pseudoaneurysm	15	Coiling
10	Posterior cerebral artery	Dissecting pseudoaneurysm	21	Expiration prior to treatment

hematoma following microsurgical clipping. Clinical outcomes at discharge were as follows: mRS 0–2 in 7 patients (70%); mRS 3 in 1 patient (10%), and mRS 6 in 2 patients (20%) (Table 1). Both patients who died presented with high-grade SAH, did not improve after several days, and eventually were transitioned to end-of-life care.

DISCUSSION

The influence of SARS-CoV-2 infection on cerebral aneurysm pathology and rupture risk is unknown. In this study, we describe the clinical characteristics of patients with aSAH who were positive for SARS-CoV-2. A prospective cohort and natural history studies demonstrate propensity for aneurysmal rupture to occur in patients older than 50 years of age.^{23,24} In this case series, 8 of 10 patients (80%) were younger than 50 years of age. In contrast, in the International Subarachnoid Aneurysm Trial (ISAT), only about 40% of patients were younger than 50 years of age.²⁵ Likewise, in the Barrow ruptured aneurysm trial, the mean age was 53 years in the clip group and 54 years in the coil group.²⁴

Saccular aneurysms are the most common culprits of aSAH (up to 90% of cases), and large size increases rupture risk.^{13,26} Of the 6 cases of saccular/blister aneurysms reviewed at our institutions, there were 4 that were 4 mm in diameter or less. The expected rupture rate for saccular aneurysms <5 mm in size is exceedingly low, i.e., less than 1% over a 5-year interval.¹³ While small aneurysms can rupture,²⁷ it is noteworthy to have such a high proportion of very small aneurysms (1.5 mm, 3 mm, 3 mm, and 4 mm) in a small series.

Our study also includes 4 dissecting pseudoaneurysms and 1 blister aneurysm, together representing 50% of the cases. Dissecting and blister aneurysms are less-common causes of aSAH than saccular aneurysms.¹¹ Precise estimates are difficult, but most studies report dissecting pseudoaneurysms and blister aneurysms to each represent approximately only 1% of cerebral aneurysms^{28–32}; therefore, it is noteworthy to have such a high frequency of these lesions in a small case series. The pathophysiology of dissecting pseudoaneurysms differs from saccular aneurysms as it involves a defect in the internal elastic lamina followed by mural dissection and pseudoaneurysm formation. The

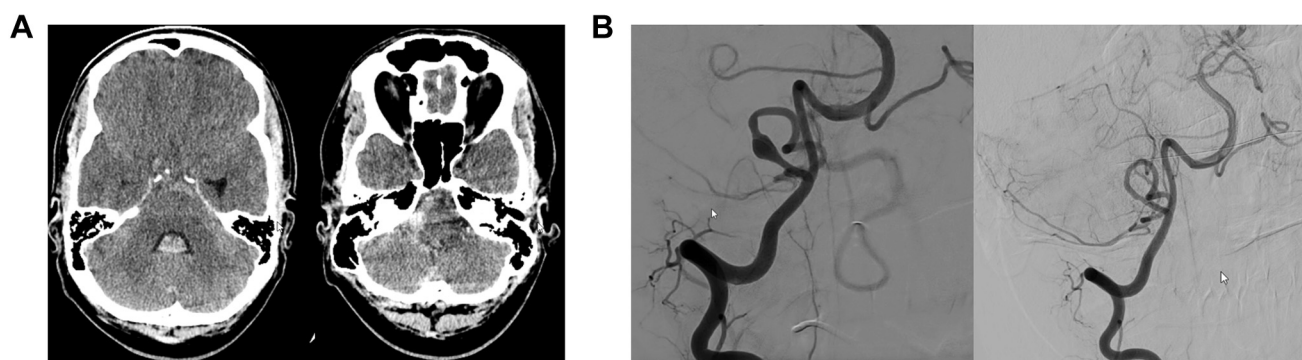


Figure 2. (A) A young patient with recent onset of cough presented with a severe headache and lethargy; computed tomography of the head showed subarachnoid hemorrhage and intraventricular hemorrhage. Patient tested positive for severe acute respiratory syndrome coronavirus 2 upon

admission. (B) Right vertebral artery angiography showing a dissecting pseudoaneurysm of the posterior inferior cerebellar artery. A Pipeline embolization device was deployed to treat the lesion. Six-month follow-up angiography showed complete aneurysm resolution.

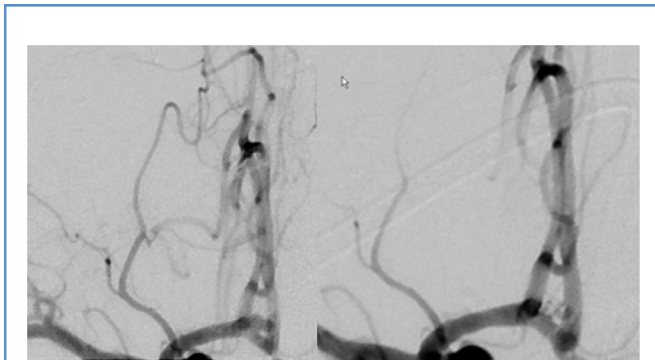


Figure 3. A young patient presented with a severe headache and lethargy/confusion. The patient was also experiencing a sore throat, cough, and a low-grade fever and tested positive for severe acute respiratory syndrome coronavirus 2 upon admission. Right internal carotid artery injection showing a 3-mm anterior communicating artery aneurysm, which was successfully coiled.

potential association seen in this series between COVID-19 and dissecting pseudoaneurysms could be interesting but it remains to be seen how COVID-19 could contribute to intracranial artery dissection and pseudoaneurysm formation.

The influence of the COVID-19 pandemic on access and delivery of healthcare is a potentially influential variable in our study. There was a decrease in admissions for SAH and ruptured aneurysm embolization procedures during the pandemic,³³ consistent with the notion that pressures on the health care system and public avoidance behaviors caused a decline in healthcare access.³⁴ Further, we did not collect patient history of connective tissue disorders or recent head trauma, both of which can cause dissecting aneurysms.^{35,36} These factors could potentially influence the number or characteristics of the patients included in this series. In contrast, it is reassuring that the outcomes in our cases do not seem to differ from what is expected with aSAH. Three of 10 patients had an mRS of >2 at discharge, which is consistent with existing literature.²⁴

The current study is not designed to establish a causality between COVID-19 and cerebral aneurysm rupture; instead, it is meant to describe and analyze the characteristics of ruptured aneurysms in patients with COVID-19. Given the high incidence of small aneurysm ruptures in young patients in this series, one could speculate that—in a subset of patients—the inflammatory response accompanying COVID-19 may cause the premature rupture of preexisting saccular cerebral aneurysms that would have otherwise ruptured at a later age when they have grown larger in

size. We suggest that any relationship between SARS-CoV-2 infection and cerebral aneurysm rupture could possibly involve macrophage-mediated production of interleukin-1 β , interleukin-6, and tumor necrosis factor- α . Macrophages are actually highly implicated in both aneurysmal rupture and COVID-19–related inflammations.^{17,37,38} This remains, however, purely speculative and warrants additional investigation. A larger sample of patients with aSAH and measurement of inflammatory mediators would be especially valuable in defining the association between SARS-CoV-2 infection and aSAH.

CONCLUSIONS

Over 1-year into the COVID-19 pandemic, the global community is constantly discovering sequelae of SARS-CoV-2 infection. In this case series, we report 10 aSAH cases that occurred in patients positive for SARS-CoV-2. These cases are the first case series of this specific phenomenon and they raise questions on a possible interaction between SARS-CoV-2 infection and cerebral aneurysm rupture. The atypical features, namely small size, presence of dissection, and young age, deserve further study.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

William S. Dodd: Data curation, Formal analysis, Writing – original draft. **Pascal M. Jabbour:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Ahmad Sweid:** Data curation, Formal analysis, Writing – review & editing. **Stavropoula Tjounakaris:** Data curation, Formal analysis, Writing – review & editing. **Michael R. Gooch:** Data curation, Formal analysis, Writing – review & editing. **Fadi Al Saiegh:** Data curation, Formal analysis, Writing – review & editing. **David M. Hasan:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Robert M. Starke:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Peter T. Kan:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Adam J. Polifka:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Dimitri Laurent:** Data curation, Formal analysis, Writing – original draft. **Katharina M. Busl:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Ritam Ghosh:** Data curation, Formal analysis, Writing – review & editing. **Brian L. Hoh:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. **Nohra Chalouhi:** Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing.

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