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Case Report

Ruptured cerebral aneurysms in COVID-19 patients: A review of literature with case examples

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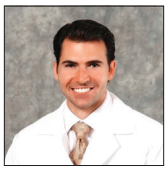

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ABSTRACT

Background: The novel severe acute respiratory syndrome coronavirus 2 is responsible for over 83 million cases of infection and over 1.8 million deaths since the emergence of the COVID-19 pandemic. Because COVID-19 infection is associated with a devastating mortality rate and myriad complications, it is critical that clinicians better understand its pathophysiology to develop effective treatment. Cumulative evidence is suggestive of cerebral aneurysms being intertwined with the hyperinflammatory state and hypercytokinemia observed in severe COVID-19 infections.

Case Description: In case example 1, the patient presents with chills, a mild cough, and sore throat. The patient develops high-grade fever of 39.8° C, decreased oxygen saturation of 93% on room air, and an extensive spontaneous subarachnoid hemorrhage (SAH) in the basal cisterns from a ruptured left posterior communicating artery aneurysm. In case example 2, the patient presents with a positive PCR test for COVID-19 2 weeks prior with spontaneous SAH and found to have a large multilobulated bulbous ruptured aneurysm of the anterior communicating artery. Both patients' symptoms and high-grade fever are consistent with hypercytokinemia and a hyperinflammatory state, with elevated granulocyte colony-stimulating factor, inducible protein-10, monocyte chemoattractant protein-1, M1P1A, and tumor necrosis factor-α inflammatory mediators found to be elevated in COVID-19 intensive care unit admissions.

Conclusion: COVID-19 effect on cerebral aneurysms requires future studies to clearly delineate correlation, however, hypercytokinemia and a hyperinflammatory state are strongly implicated to cause degenerative vascular changes that may predispose patients to cerebral aneurysm formation, change in size or morphology, and resultant aneurysm rupture.

Keywords: Aneurysm rupture, Cerebral aneurysms, COVID-19, Subarachnoid hemorrhage

INTRODUCTION

To date, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for over 83 million reported cases and over 1.8 million deaths globally since the beginning of the pandemic.[24] The devastating mortality rate and myriad associated complications SARS-CoV-2 infection constitute a dire need for effective prevention and treatment options. Accumulating evidence is suggestive of cerebral aneurysm rupture being intertwined with the pathophysiology

of COVID-19.[4] Pathophysiologically, cerebral aneurysm rupture is characterized by deterioration of the media, loss of internal elastic lamina, and a resulting degradation of the arterial wall.[5,22] Of those with an aneurysm, the estimated risk of rupture is 1% annually.[15] Subarachnoid hemorrhage (SAH) resulting from a ruptured aneurysm is a serious complication with a mortality between 45% and 65%.[23] About 12% of these mortalities occur immediately.[8] In cases of SAH rupture survival, 20% of individuals are dependent on help for daily living activities.[15]

Although current literature has yet to delineate an exact and definite relationship between COVID-19 and cerebral aneurysm formation/rupture, literature and data of other similar inflammatory states and vascular injury have illuminated several possible explanations of well-described changes observed in other disease processes that can explain COVID-19 pathogenesis. The virus has been reported to bind surface angiotensin-converting enzyme 2 (ACE-2) receptor to enter cells, thus making the virus capable of causing endothelial injury.[4] Endothelial injury may lead to direct or indirect endothelial toxicity which can explain arterial wall deformation and aneurysm formation or rupture in COVID-19 patients.[4] Direct endothelial toxicity can result from endothelial cell invasion or through cytokine recruitment, activation of prothrombin factors and coagulation cascades, and complement-mediated microvascular thrombosis.[4] In addition, tight junction protein disturbance caused by the endothelial toxicity can lead to a weakened blood–brain barrier (BBB), further predisposing one to aneurysm formation or rupture.[4] All aforementioned pathologic changes offer explanations to COVID-19 pathogenesis, cerebral aneurysm formation, and rupture. Hence, these changes will be discussed in further detail as the focus of this discussion.

Pathophysiology of cerebral aneurysm

In addition to vessel wall shear stress, the regulation of healthy vasculature involves different cell types and their regulation of local factors, some of which fall out of equilibrium leading to degenerative changes observed in the damaged and weakened vasculature of cerebral aneurysms. Wall shear stress has been linked to the activation of Rac1 and several downstream factors involved in the response to the increased flow and wall shear stress.[21] Tzima *et al*. concluded that Rac1 activation is a major factor within endothelial cell adaptation to increased wall shear stress, leading to changes in cytoskeletal reorganization and gene expression. Rac1 is known for its effects in producing reactive oxygen species and upregulating inflammatory factors such as nuclear factor kappa B (Nf-KB).[21] Nf-KB has been identified as in important inflammatory mediator in other studies, where inhibition of the Nf-KB pathway had an inhibitory effect on the formation of cerebral aneurysms, further suggesting that inflammation and the effects of Nf-KB are responsible for predisposition to intracerebral hemorrhage (ICH) in COVID-19-positive patients.[2]

Downstream effector proteins such as monocyte chemoattractant protein-1 (MCP-1) play a major role in the pathogenesis of cerebral aneurysms by recruiting monocytes and macrophages to the area.[3] MCP-1 is induced as part of the Nf-KB pathway and the induction of MCP-1 results in the release of pro-inflammatory cytokines and proteinases, which promote the pathogenic and degenerative changes seen in aneurysmal walls.[3] Alg *et al*. highlighted the contribution of matrix metalloproteinase (MMP) dysregulation as an important factor responsible for degenerative remodeling seen in vascular walls, as it causes breakdown of extracellular matrix proteins such as elastin, collagen, and laminin. An association between mutations in MMP-2 and aneurysm formation has been established, with dysregulation of MMPs resulting in either excessive, or scant breakdown of the ECM proteins.[1]

Vascular smooth muscle cells (VSMCs) are critical not only to the normal integrity of the vasculature but also for their role in the pathological development of cerebral aneurysms. VSMCs are highly specialized contractile cells which function to maintain normal vessel morphology and blood pressure.[11] VSMCs can switch their phenotype in response to certain stimuli, which changes the expression levels of certain key structural proteins. More specifically, endothelial injury leads to VSMC phenotype switching, involving a shift away from the contractile to a pro-inflammatory phenotype, decreasing the production of important contractile proteins, and increasing the expression of inflammatory mediators such as tumor necrosis factor (TNF)-a and MMPs.[11] Other studies have described similar changes as dedifferentiation where a degenerative process resulted in the loss, disorganization, and a pathologic stretching of medial smooth muscle cells.[16] Other studies have also found disruption of the smooth muscle cell layers in samples taken from ruptured cerebral aneurysms, where the normal vascular structure was replaced by hyaline-like structures.[10]

Pathophysiologic changes from COVID-19

Cumulative recent evidence suggests that a subgroup of patients with severe COVID-19 infections is observed to have a cytokine storm syndrome. Identification of these patients with hyperinflammatory state and subsequent cytokine storm followed by appropriate treatment with therapeutics that are currently prescribed to treat other diseases may reduce mortality rates of severe COVID-19 infection.[12] The purpose of this section is to illuminate a relationship between the hyperinflammatory state observed in severe COVID-19 infections and deterioration of the vascular integrity

which, in conjunction with the undermentioned observed case examples, suggests that certain cerebral vasculature changes in severe COVID-19 infections are responsible for precipitating cerebral aneurysm formation and rupture. This notion serves to illuminate important observations and point toward questions for future studies to further the understanding of COVID-19 infections, pathogenesis, and appropriate treatment.

The current standard practice for the management of COVID-19-positive patients is solely supportive, and the leading cause of mortality in these patients is respiratory failure, secondary to severe acute respiratory distress syndrome (ARDS).[20] In ARDS, the pathophysiology is such that damage to the capillary endothelium and alveolar epithelium causes increasingly impaired removal of fluids which ultimately results in accumulation of exudative, protein-rich fluid within the alveolar space.[18] Within the alveolar airspace, this exudative fluid causes diffuse alveolar damage and a subsequent release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF – a combination of cytokines that may be the culprit for a hyperinflammatory state and cytokine storm that compromises the integrity of the vasculature. Recent studies have demonstrated IL-1beta, TNF-alpha, and IL-8 cytokine levels to be elevated in bronchoalveolar lavage fluid of patients with established ARDS secondary to severe COVID-19 infection. One additional consideration is that these pro-inflammatory cytokines recruit neutrophils to the lungs, activated once they transmigrate across the vasculature, and begin to release toxic mediators such as reactive oxygen species and proteases.[13]

Inflammation due to neutrophil activation is the key to the development of the hyperinflammatory state in which activation of the protein transcription factor NF-kB mediates foundational changes in DNA transcription.[13] This protein complex transcription factor will control many of the DNA transcription changes that result in expression of the genes for many elevated pro-inflammatory mediators found in ARDS patients.[18] Furthermore, the continuing activation of NF-kB in patients with established ARDS is highly suspected to be responsible for both the cause and the effect of the continuing inflammatory response and persistent elevation in expression of pro-inflammatory cytokines and other mediators present in ARDS patients within a clinical setting.[13]

Secondary hemophagocytic lymphohistiocytosis (sHLH) is an under acknowledged hyperinflammatory syndrome that shares a similar cytokine profile with severe COVID-19 infections, implying an analogous pathophysiology process (Mehta *et al*., 2020). Most notably, IL-2, IL-7, granulocyte colony-stimulating factor (GCSF), interferon-γ (IFN-γ), inducible protein 10 (IP-10), MCP-1, macrophage inflammatory protein 1-α (MIP-1α), and TNF-α are the primary mediators of inflammation which are found to be increased in patients with sHLH.[12] Clinically, sHLH is particularly characterized by a fulminant and often times lethal hypercytokinemia that results in multiorgan failure. In resemblance to the hypercytokinemia profile observed in sHLH, a hypercytokinemia of IL1-1 beta, IFN-γ, IP-10, and MCP1 has been noted in patients infected with COVID-19, and in particular, COVID-19 patients requiring intensive care unit (ICU) admission had higher concentrations of GCSF, IP-10, MCP-1, M1P1A, and TNF-α than patients who did not require ICU admission. These findings suggest that cytokine storm of these pro-inflammatory mediators is associated, or perhaps even responsible for more severe cases of COVID-19 infection, and that the inflammatory state of these detrimental cases is analogous to sHLH.[7] In mice models, the aforementioned MCP-1 has been demonstrated to mediate a significant role with CA formation and macrophage accumulation. Because MCP-1 levels are found to be elevated in patients requiring ICU admission, it is indicative that these same patients with hypercytokinemia and elevated MCP-1 are also predisposed to CA formation and ICH, again linking hyperinflammation to disruption of the cerebral vascular integrity.[3]

In consideration of the aforementioned, the hyperinflammatory state and particular hypercytokinemia profile are implicated to be responsible for or at the very least, associated with the mechanism by which severe COVID-19 infection degrades the integrity of the vasculature. Inflammatory states will cause the release of other factors such as endothelin-1, angiotensin-II, and phospholipase A-2 which trigger vasoconstriction of the damaged vessel, increased vascular permeability, and the destruction of microvascular architecture, ultimately amplifying the effects of inflammation and consequent lung damage.[18] One proposed explanation for the connection between cytokine storm and a weakening of arterial vasculature proposed by Kandula *et al*. is that the hypercytokinemia of pro-inflammatory cytokines and cytotoxic cells in sHLH may result in endothelial injury through increased vascular permeability, resultant ischemia of the vascular endothelium, and cell damage.[9] In another compelling experimental study by Moriguchi *et al*., cytokine cascade has been directly demonstrated to be responsible for neurological disorders and acute cerebrovascular disease.[6] This loss of integrity in the vasculature due to the cumulative effects of ischemia, rigorous vasoconstriction of the damaged vessel and resultant increase in shear wall stress, increased vascular permeability, destruction of microvasculature architecture, release of proteases, and reactive oxygen species which all occur during states of hyperinflammation makes a compelling case for a mechanism by which the arterial cerebral vasculature in the Circle of Willis is left predisposed to aneurysm formation and rupture in patients with the particular aforementioned

hypercytokinemia profile secondary to severe COVID-19 infection.

One final major consideration is the systemic effects of COVID-19 infection. COVID-19 infection occurs through the SARS-CoV-2 virion binding ACE-2, an enzyme critical for regulation of blood pressure and anti-atherosclerotic effects. Consistent with these other findings, SARS-CoV-2-ACE-2 binding has been demonstrated to be responsible for direct damage to the BBB in two separate studies.[17,19] On a systemic level, this may result in elevated blood pressure, which even further accelerates formation of cerebral aneurysm and ICH. From the aforementioned findings across myriad studies, severe COVID-19 infections and hypercytokinemia are highly implicated to cause deterioration of the arterial vasculature and are found to be a likely culprit for vascular changes resulting in the formation and rupture of intracranial aneurysms.

CASE EXAMPLES

Case example 1

A 52-year-old Hispanic male presented from an outside hospital with head computed tomography (CT) concerning for spontaneous SAH. The patient was initially brought to an outside hospital after he was found unresponsive by his family following a bout of coughing earlier that morning. CPR was initiated for 5 min before EMS arrival, with the patient experiencing a single episode of vomiting and bladder incontinence before regaining consciousness. His family noted that the patient had complaints of chills, a mild cough, and sore throat the night before admission but was otherwise he was in his normal state of health. He had no history of prior tobacco use and otherwise had a medical history significant for hypertension without current pharmacologic treatment. There was no family history of aneurysms or any reported viral prodrome within his family contracts. His baseline modified Rankin scale (MRS) was 0.

On arrival to our institution, the patient had no complaints other than a mild headache and neck pain. Initial vitals were significant for a temperature of 39.8° C, blood pressure 157/95 mmHg, and oxygen saturation of 93% on room air. Clinical examination was notable for some mild confusion, but otherwise there were no cranial nerve deficits or focal findings on clinical exam. A noncontrast head CT demonstrated extensive SAH in the basal cisterns around the midbrain extending into the left Sylvian fissure with mild prominence of the bilateral temporal horns [Figure 1]. CT angiogram (CTA) of head and neck demonstrated a small left posterior communicating (p-comm) aneurysm [Figure 2] along with bilateral airspace disease at the lung apices, compatible with pneumonia [Figure 3]. An incidental, small right cavernous segment aneurysm and anterior communicating segment fusiform dilation were also noted. Clinical grading was consistent with a Hunt-Hess grade of 1+1 (hypertension) and modified Fisher grade of 3. Laboratory values showed no leukocytosis, platelets 125 10e9/L, sodium 135 mEq/L, BUN 14 mg/dL, and Cr 0.7 mg/dL. Liver function and coagulation studies were within normal ranges except for d-dimer, which was elevated at 1.4 mg/L (UNL 0.59) and fibrinogen, elevated at 451 mg/dL (UNL 440). Coronavirus PCR was positive.

An external ventricular drain was placed with an opening pressure 21 mmHg. The patient was intubated before being taken to the neurointerventional suite for treatment. Diagnostic cerebral angiography of the left internal carotid artery (ICA) revealed a dominant left p-comm artery filling the posterior cerebral artery on the left with small aneurysm

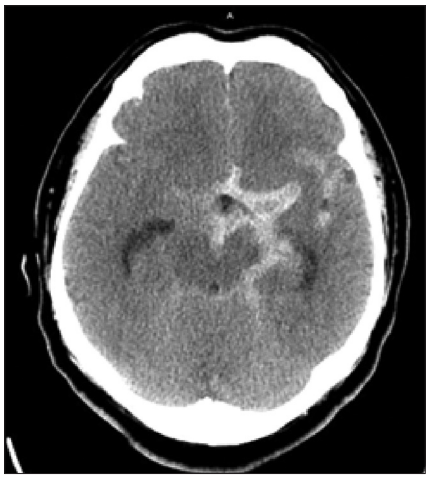

Figure 1: Initial axial noncontrast head CT demonstrating SAH in the basal cisterns extending into primarily the left Sylvian fissure with mild prominence of the temporal horns bilaterally.

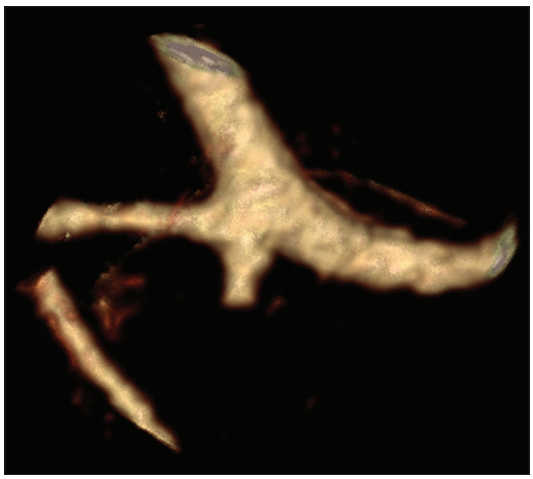

Figure 2: CTA head with contrast of the left ICA with 3D reconstruction demonstrating left posterior and interior projecting aneurysm.

emanating from the junction of the left ICA and left p-comm artery, pointing posteriorly and inferiorly measuring 4 × 6 × 4 mm [Figure 4]. There was no daughter sac or evidence of extravasation of contrast. A total of six Gugliemi detachable coils (GDCs) were placed within the aneurysm leading to >95% aneurysm obliteration. A total of six Gugliemi detachable coils (GDCs) were placed within the aneurysm leading to > 95% aneurysm obliteration [Figure 5].

The patient tolerated the procedure well. He was extubated and taken to the neurological ICU (NICU) in stable condition where he was monitored for complications of SAH. A 10-day course of empiric antibiotics was completed for aspiration pneumonia. Over the course of his stay, his neurological status remained stable, however, he developed progressive hypoxemic respiratory failure and required intubation on hospital day 4 (postbleed day 3). Convalescent plasma and dexamethasone at 6 mg daily were initiated on hospital day 4, while remdesivir was held as the replication phase had passed. His initial high PEEP and FiO_2 demands were weaned and he was successfully extubated on hospital day 15 and his ventricular drain removed on hospital day 13. He had no evidence of vasospasm and was downgraded from the ICU on hospital day 16. Clinically at the time of downgrade, the patient was GCS14, e4v4m6, with some intermittent confusion but otherwise appropriate without cranial nerve or any lateralizing motor deficit.

Case example 2

A 61-year-old Hispanic male was transferred from an outside facility when he was found by his wife after falling in the bathroom earlier that morning. At the outside institution, he reportedly had a GCS of 8 (unknown breakdown) and was for declining mental status. CT head demonstrated prominent SAH in the basal cisterns [Figure 6] and CTA demonstrated a bilobed anterior communicating artery aneurysm [Figure 7]. Clinical grades demonstrated HH4+1 and mFG4. His medical history was significant for hypertension, previous craniotomy from a gunshot wound to the head, prior heroin abuse, and hepatitis C. He had tested positive for COVID-19 approximately 2 weeks before admission, though

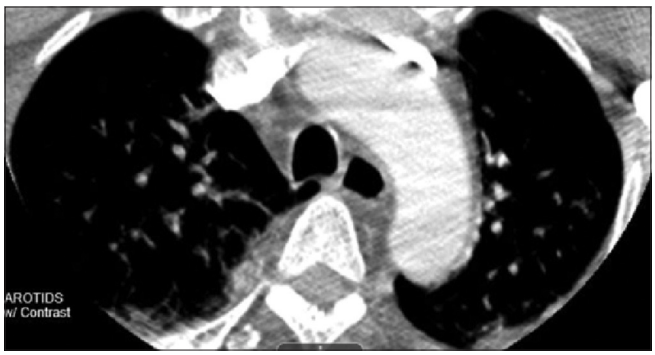

Figure 3: Axial CT through the lung apices demonstrating multifocal bilateral airspace disease compatible with pneumonia.

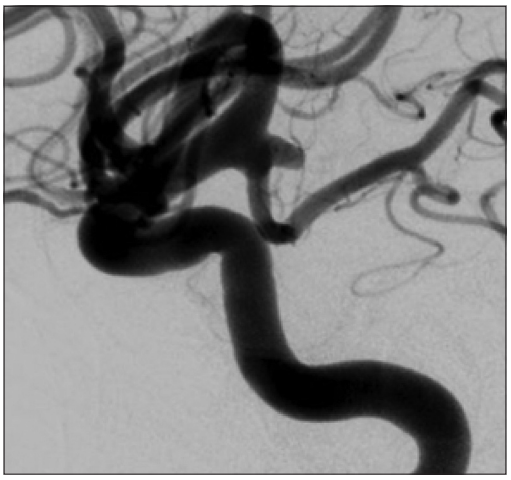

Figure 4: Lateral cerebral angiogram of the left ICA demonstrating left posterior and interior projecting aneurysm.

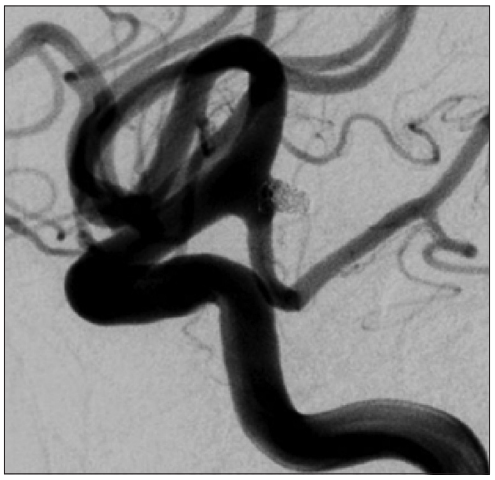

Figure 5: Lateral cerebral angiogram of the left ICA demonstrating coiled aneurysm with no residual filling.

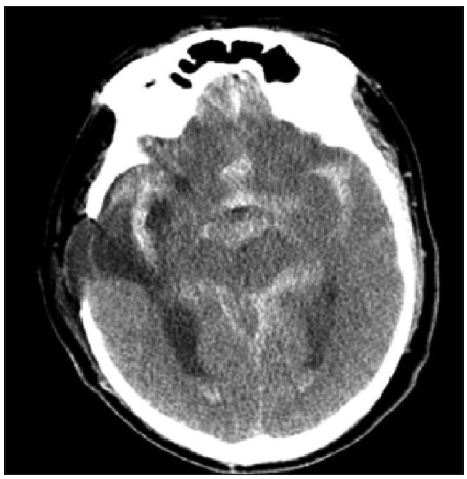

Figure 6: CT head without contrast demonstrating prominent blood in the basal cisterns and Sylvian fissure bilaterally with the right temporal encephalomalacia and cranial defect from previous gunshot wound to the head.

asymptomatic. Baseline MRS was 0 with no family history of aneurysms.

On arrival to our institution, he was afebrile, with BP 164/100 mmHg and saturating 100% on 40% FiO_2. Clinically, he was intubated with a GCS of 8T (e2vTm5), with a prosthetic right eye but otherwise with intact cranial nerves. He was localizing to pain in his left upper extremity and withdrawing in all other extremities. Laboratory values were significant for leukocytosis of 18.0 10e9/L and sodium 135 mEq/L. Liver function test and coagulation were within normal limits. A right frontal ventriculostomy was placed and he was started on levetiracetam, nimodipine, and high-dose rosuvastatin for vasospasm protection.

On postbleed day 1, he was taken to the interventional suite for coiling. Diagnostic angiography of the left ICA revealed a large multilobulated bulbous aneurysm of the anterior communicating artery [Figure 8]. Coil embolization was successful with complete aneurysm obliteration with minimal contrast filling along the neck and no evidence of occlusion of either the communicating segment or the distal A2's or proximal A1 segments right and left sides [Figure 9].

Postprocedure, the patient returned intubated to the ICU with a stable neurological examination. He was successfully extubated on hospital day 2 and spiked a fever on hospital day 5–38.4°C, but otherwise remained afebrile during his hospital course. Ventricular drain weaning was unsuccessful and a right frontal ventriculoperitoneal shunt was placed on hospital day 20. He was downgraded from the ICU on hospital day 22 with no evidence of vasospasm. Clinically, he was a GCS of 14, e4v4m6. He would intermittently converse but remained confused. Cranial nerves were intact and he would intermittently follow simple commands in all extremities with no lateralizing motor deficits.

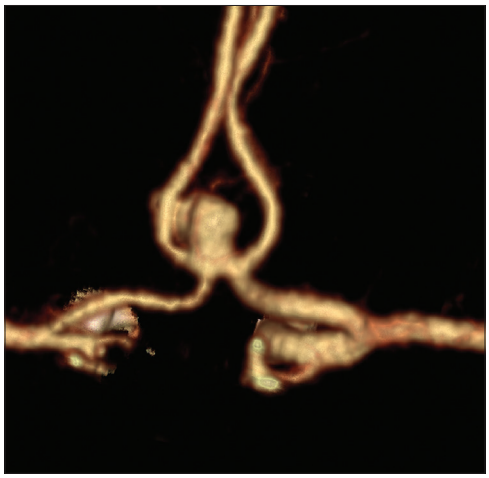

Figure 7: CTA head demonstrating bilobed anterior communicating artery aneurysm with 3D reconstruction.

Future considerations

With the onset of the SARS-CoV-2 pandemic, the novel virus leaves much to discover between COVID-19 and ruptured cerebral aneurysms. Further studies should be performed to evaluate the incidence of cerebral aneurysms in the COVID-19 population compared to general population or non-COVID-19 population to assert if there are any statistically significant differences. Large retrospective studies at institutions that have access to database logging will be required to follow trends and analyze the data. Finding patients with pre- and post-COVID-19 inoculation would also prove useful to detect if the ruptured cerebral aneurysms were present beforehand or there was any change in size or morphology after becoming infected.

The immune response in COVID-19 infection is a likely culprit in the predisposition to cerebral aneurysm formation or changes in size, morphology, and tendency to rupture through NF-Kb expression causing markedly increased cytokine release, "cytokine storm," induced ARDS and sHLH. Severe COVID-19 cases may benefit from IL-6 pathway inhibition, as a retrospective study of COVID-19 patients found nonsurvivors to have elevated IL-6 and serum ferritin levels.[20] There are currently clinical trials

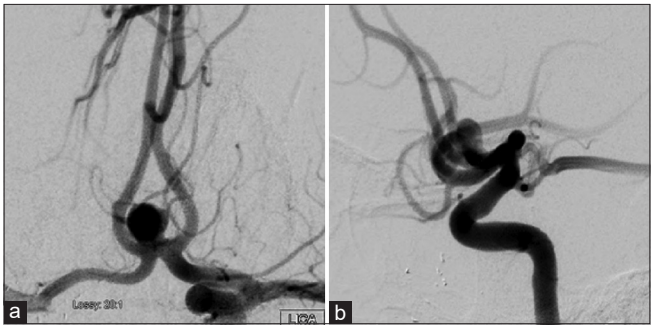

Figure 8: AP (a) and lateral (b) cerebral angiogram projections of the left ICA demonstrating bilobed ACOM aneurysm.

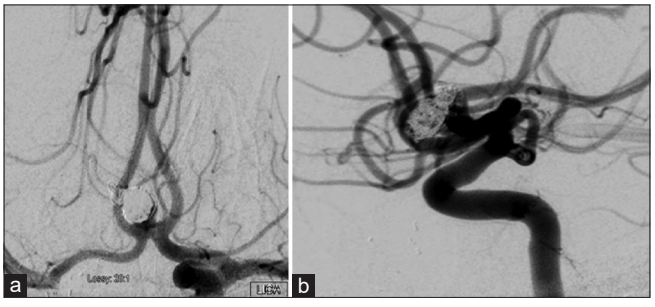

Figure 9: AP (a) and lateral (b) cerebral angiograms of the left ICA demonstrating successful coil embolization of the ACOM aneurysm with minimal residual filling along the neck.

underway to test IL-6 antagonists, IL-6R antagonists, and tocilizumab for the management of COVID-19 patients with severe respiratory complications.[14] However, these states of hyperinflammation and appropriate therapies which attenuate the hyperinflammatory state will be important areas for future studies.

CONCLUSION

The direct impact of COVID-19 on cerebral aneurysm formation and rupture is still unclear, however, certain biochemical inflammatory processes could be the link. We have identified two case examples. The patient in case example 1 presented to our institution due to SAH secondary to ruptured p-comm aneurysm. The patient had no family history of aneurysms and had no significant risk factors other than hypertension. He tested positive for COVID-19 on inpatient testing.

In the second case example, the patient presented to the hospital with declining mental status and CT confirmed prominent SAH in the basal cisterns. The patient had tested positive for COVID-19 2 weeks prior, thus one could speculate that his anterior communicating aneurysm could be a symptom of his COVID-19 infection. Although seemingly asymptomatic during initial infection, the patient had severe leukocytosis, thus indicating serious COVID-19 infection. Serious infection is implicated in arterial vasculature damage. However, the patient also had a severe hypertension history, which also may have contributed to aneurysm rupture.

The inflammatory response from COVID-19 induces hypercytokinemia and therefore has been implicated to degrade the integrity of the cerebral vasculature and predispose individuals to cerebral aneurysm formation, rupture, and ICH. Therefore, these case examples along with the literature review highlight important areas for future studies on COVID-19-associated hyperinflammatory state, pathophysiology, and effective treatment. At current time, most of the link between COVID-19 and cerebral aneurysm formation, changes, or rupture are speculation and long-term retrospective studies will be needed to assess for certainty.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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