Fulminant Extra- And Intracranial Arteriovenous Thrombosis And Non-aneurysmal Subarachnoid Hemorrhage Following COVID-19 Infection

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Abstract

Purpose: Coronavirus disease of 2019 (COVID-19) is associated with increased risk of stroke and intracranial hemorrhage. This first report of fulminant panvascular arteriovenous thrombosis with subarachnoid hemorrhage (SAH) in a post-COVID-19 infection is attributed to extensive arteriovenous inflammation leading to arterial rupture following vasculitis.

Case Report: We report a rare case of extensive extra- and intra-cranial cerebral arteriovenous thrombosis following COVID-19 infection, presenting as fatal non-aneurysmal subarachnoid hemorrhage. The clinical course, biochemical and radiological evaluation is discussed. The other possible etiological differentials which were analysed and ruled out during case management are also detailed.

Conclusion: A high degree of suspicion for COVID-19 induced coagulopathy leading to extensive non-aneurysmal, non-hemispheric SAH and malignant intracranial hypertension should be entertained. Our experience and previous reports on non-aneurysmal SAH in such patients show a poor prognosis.

Keywords: arterial thrombosis; basilar artery; COVID-19; non-aneurysmal SAH; superior sagittal sinus

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INTRODUCTION

Since it was first reported in late 2019, the novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) reached pandemic proportions and has devastated the global landscape. After many initial reports confirmed the predisposition to thrombosis in COVID-19 patients, reports of hemorrhage occurring in multiple organ systems including the central nervous system have emerged[1-4]. The virus infects endothelial cells causing inflammation and endotheliitis[3,5]. The resultant vascular inflammation, platelet dysfunction and stasis leads to a prothrombotic state causing extensive thrombosis affecting the arterial and venous system[2,4,6,7].

CASE REPORT

A 32-year-old lady with no co-morbidities presented

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with headache of increasing severity over 2 days duration leading to loss of consciousness. She presented to the emergency room with a Glasgow coma scale of 5/15. She underwent emergent intubation and a non-contrast computed tomography (CT) brain scan showed modified Fisher grade 3 subarachnoid hemorrhage (SAH) and hydrocephalus (Fig 1A). Multiple small eccentric thrombi were also seen in the superior sagittal sinus (Fig 1B). No aneurysm or arteriovenous malformation was discernible on the CT brain and neck angiogram. The upper basilar artery was not visualised due to thrombosis (Fig 2). There were multiple small eccentric thrombi in mid-basilar, bilateral vertebral and internal carotid arteries (Figures 2 and 3), causing luminal occlusion and stenosis between 40-80% .

After the above imaging she underwent an emergent right frontal external ventricular drain placement. Digital subtraction angiography (DSA) could not be performed as her sensorium deteriorated further and she became hemodynamically unstable. A repeat CT brain scan of the brain was performed the day following external ventricular drain placement. It showed good ventricular decompression, stable SAH and a hypodense midbrain and pons. She was yet to receive the COVID-19 vaccine and on interviewing her family, a history of loss of smell, taste and malaise lasting 5 days was obtained from approximately 45 days prior to this presentation. Her COVID-19 RT-PCR test at admission was negative. A subsequent COVID-19 IgM antibody assay returned positive and the total leukocyte count, C-reactive protein (CRP) and D-dimer levels were elevated. The coagulation profile, serum LDH, ferritin and fibrinogen levels were

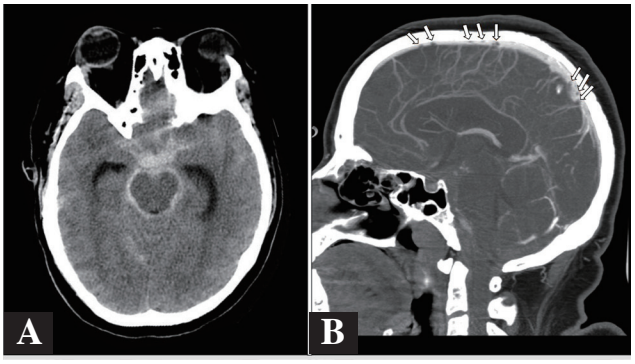

Figure 1. (A)CT head plain showing extensive subarachnoid hemorrhage; (B) CT venogram showing multiple small eccentric thrombi (arrows) in the superior sagittal sinus

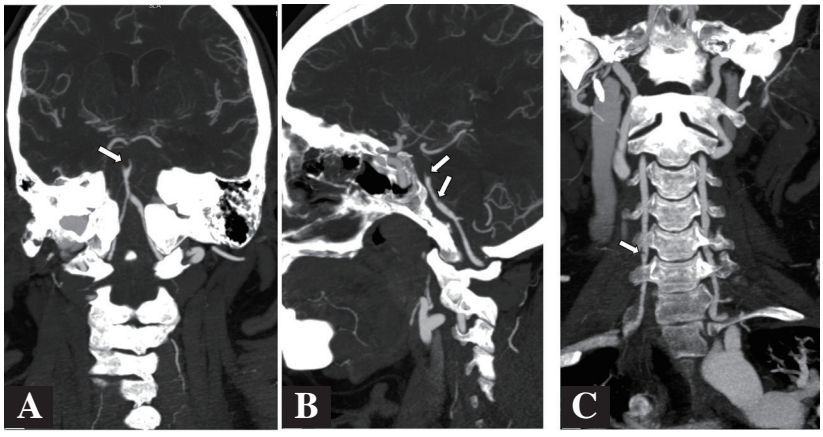

Figure 2. CT angiogram with (A) coronal reconstruction showing upper basilar thrombus (arrow) (B) sagittal reconstruction showing large upper basilar and small eccentric mid-basilar thrombi (arrows) (C) coronal reconstruction showing eccentric thrombi (arrow) in the V2 segment of right vertebral artery

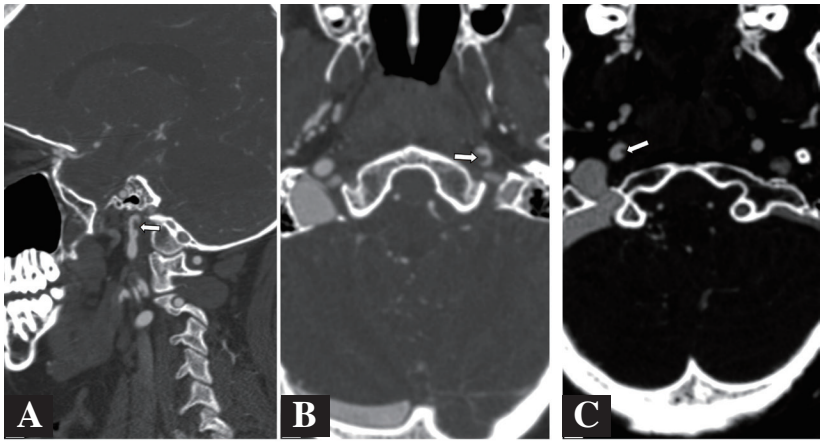

Figure 3. CT angiogram (A) sagittal reconstruction and (B) axial images showing eccentric thrombus (arrow) in the petrous segment of left ICA and (C) axial image showing small eccentric thrombus (arrow) in the right cervical ICA

Table 1. Biochemical and haematological parameters

Parameter	Value	Range
Total leukocyte count	25200 cells/cu mm	4000 to 10000
Platelet count	474000 cells/cu mm	150000 to 450000
Prothrombin time	14.1 sec	11.94-14.46
Activated partial thromboplastin time	23.9 sec	26.46-32.94
INR	1.05	
Erythrocyte sedimentation rate	45 mm/hr	1-20
D-Dimer	8.35 microgram/mL	0-0.5
CRP	21.6 mg/L	Normal < 5 mg/L
Lactate dehydrogenase	312 IU/L	180-360
Serum Ferritin	230.9 ng/mL	21.8-274.6
Anti-SARS-CoV-2 spike protein antibody	211 U/mL	Negative <0.8

within the normal range (Table 1). Blood workup for ANA, ANCA, anti-CCP antibody and blood culture were negative. She was administered levetiracetam, osmotic diuretics, nimodipine apart from dual inotropes to maintain her blood pressure. Unfortunately despite all measures, she worsened rapidly and succumbed two days after admission.

DISCUSSION

Alwan and Johnson have provided the clinical spectrum and definition of past acute COVID and long COVID illnesses[3]. There has been a relative decline in overall SAH related hospitalisations and aneurysmal SAH-related hospitalisations and during the first wave of the COVID-19 pandemic[1,2,9,10]. However, there has been a significant increase in the incidence of non-aneurysmal SAH and a marked change in disease presentation during the pandemic. Cezar-Junior et al. reported 3 out of 4 patients who presented with non-aneurysmal SAH to be infected with the COVID-19 virus at the time[5]. They analyzed the incidence of SAH in non-COVID-19 patients between the 3 months from March and May 2020 and compared it with the same interval in 2019. Though there was a 39% reduction in the number of patients hospitalized for SAH, there was a 112.5% increase in the number of non-aneurysmal SAH (34% in 2020 vs 16% in 2019)[5]. Nawabi reported a 61% incidence of SAH in 18 COVID--19 patients with hemorrhagic stroke. Fifty percent of the patients were either on anticoagulation or anti-platelet therapy. Out of 11 patients with SAH, 9 (81%) were primary, cortical and non-aneurysmal and 1 each had

concomitant acute subdural and intra-parenchymal bleeds respectively[8]. Batcik also reported a 75% incidence of non-aneurysmal SAH among 4 patients known to have Covid-19 infection. Interestingly, one of the patients had serum IgG and IgM COVID-19 antibodies but a negative RT-PCR during the first hospitalisation with fever and dyspnoea. He presented 4 months later with sudden neurological deterioration and died from a fatal SAH[4].

The various causes attributed to intracranial bleed in COVID-19 are viral endothelitis, complement-mediated thrombotic microvascular injury, cytokine abnormalities which contribute to vasoconstriction, ischaemia, hyper-coagulopathy, severe vessel weakening and rupture causing subsequent intracerebral hemorrhage[3,7,9,10]. The systemic inflammatory state is evidenced by elevated peripheral markers such as ESR, CRP, Ferritin, D-dimer and LDH[9,10]. Posterior reversible encephalopathy syndrome (PRES) with secondary hemorrhage in patients with COVID-19 infection is usually parenchymal and located along convexities. Reversible cerebral vasoconstriction syndrome (RCVS) is associated with multifocal intracranial arterial stenosis[7,9]. These entities were ruled out in our case by the location of bleed and the vascular architecture seen on the CT angiogram. Non-aneurysmal SAH due to venous thromboembolism prophylaxis is hemispheric in location and not extensive[4]. Our patient did not receive any anticoagulation and the SAH was extensive. A normal echocardiogram and negative blood cultures ruled out infectious aneurysms.

We conclude that our patient developed extensive inflammation of the large and medium sized arteriovenous vasculature leading to thrombosis at the site of endothelial damage, with the largest thrombus located at the upper basilar region. Extensive SAH can be attributed to arterial rupture from vasculitis as discussed above or secondary to venous hypertension. The extensive nature of the bleed, unstable hemodynamic status and rapid deterioration precluded any further diagnostic intervention in the form of a DSA or systemic anticoagulation following it. One limitation of the study, though in the absence of family history, is a screen for hypercoagulable state: Protein C & S, factor V Leiden.

This is the first report which documents the fulminant panvascular intracranial thrombosis and SAH with radiological images as post-COVID-19 sequelae. The management of such cases is limited to reduction of intracranial pressure with external CSF diversion procedures. Systemic anticoagulation should be administered only when vascular pathologies like aneurysm or arteriovenous malformation are ruled out. Our experience and previous reports show a guarded prognosis for such cases.

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