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Case Reports & Case Series

Cerebellar infarction requiring surgical decompression in patient with COVID 19 pathological analysis and brief review

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ABSTRACT

Background: This report and literature review describes a case of a COVID-19 patient who suffered a cerebellar stroke requiring neurosurgical decompression. This is the first reported case of a sub-occipital craniectomy with brain biopsy in a COVID-19 patient showing leptomeningeal venous intimal inflammation.

Clinical description: The patient is a 48-year-old SARS-COV-2 positive male with multiple comorbidities, who presented with fevers and respiratory symptoms, and imaging consistent with multifocal pneumonia. On day 5 of admission, the patient had sudden change in mental status, increased C-Reactive Protein, ferritin and elevated Interleukin-6 levels. Head CT showed cerebral infarction from vertebral artery occlusion. Given subsequent rapid neurologic decline from cerebellar swelling and mass effect on his brainstem emergent neurosurgical intervention was performed. Brain biopsy found a vein with small organizing thrombus adjacent to focally proliferative intima with focal intimal neutrophils.

Conclusion: A young man with COVID-19 and suspected immune dysregulation, complicated by a large cerebrovascular ischemic stroke secondary to vertebral artery thrombosis requiring emergent neurosurgical intervention for decompression with improved neurological outcomes. Brain biopsy was suggestive of inflammation from thrombosed vessel, and neutrophilic infiltration of cerebellar tissue.

1. Introduction

The first reported case of COVID-19 was reported to the WHO in December 2019 [1]. Large vessel stroke has been shown to be a presenting sign or complication of SARS-Cov-2 infection [2]. Oxley et al reported five large vessel stroke in patients, with four requiring neuroendovascular intervention, including one patient that also required neurosurgical intervention (hemicraniectomy) [2]. We report the first case of COVID-19 vertebral artery thrombosis related cerebellar circulation stroke requiring suboccipital decompressive craniectomy.

2. Case presentation

This is a 48-year-old African American male with diabetes, hypertension, untreated latent tuberculosis, who presented with one week history of fevers, cough, shortness of breath, and hypoxia. The patient had a prior history of tuberculosis for which he had not been treated for and had not shown active disease on prior chest x-rays. Initial and hospital clinical characteristics are shown in Supplementary Table 1. The patient tested positive for COVID-19 on presentation with detection of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) viral ribonucleic acid from a nasopharyngeal swab specimen using the Cepheid Xpert Xpress SARS-Cov-2 rapid 30 min Real-time Polymerase

Abbreviations: ARDS, acute respiratory distress syndrome; BiPaP, Bilevel positive airway pressure; COVID-19, Corona Virus Disease 2019; CP, cerebellopontine; CRP, C-reactive protein; CT, computed tomography; CTA, CT angiography; CXR, chest X-ray; FiO2, fraction of inspired oxygen; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; STAT, statum which is Latin meaning immediately; t-PA, tissue plasminogen activator; WHO, World Health Organization

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Patient initial chest x-ray shown in Fig. 1.

Fig. 1. Chest X-Ray on admission: Multifocal pulmonary consolidative opacities are present.

H.N. Patel, et al. Interdisciplinary Neurosurgery 22 (2020) 100850 daily for 5 days for moderate ARDS. His interleukin-6 levels were also checked and these were elevated at 555 pg/ml. The remainder of the patient’s stroke work up did not identify any abnormal cardiac rhythm, cardiac embolus, dissection, or athero-sclerotic disease process. Over the next 48 h, on day 6, and day 7 of admission, his mental status declined further and he was intubated. A repeat CT of the head showed increasing mass-effect on the fourth ventricle in the right cerebellar hemisphere, with effacement of the CP angle cistern and midline shift (Fig. 2C, D).

On hospital day 9 patient had Cushing response (hypertension with bradycardia) indicating an increase in the intracranial pressure with STAT consultation of neurosurgery by the primary team. The systolic blood pressure increased to 182 mmHg and heart rate decreased to 52 beats per minute. STAT CT head showed left cerebellar stroke with mass effect on the fourth ventricle and obliteration of the paramesencephalic cistern. No gross hydrocephalus (Fig. 2E). Due to the patient rapid clinical decline, Cushing response, and radiographic findings of mass effect on the brainstem it was decided the patient would need emergent cerebellar decompression and placement of an external ventricular drainage catheter in order to alleviate intracranial hypertension. The neurologic decline was attributed to increased cerebellar edema secondary from the original stroke event. The Patient was given weight dosed Protamine 7.5 mg to reverse the heparin gtt and mannitol in anticipation for emergent suboccipital craniectomy and placement of right external ventricular drain for intracranial pressure (ICP) monitoring and drainage. The surgery was performed under COVID-19 precautions in a negative pressure operating room and all staff wore Powered Air Purifying Respirator (PAPR) throughout the case and with all clinical interactions with the patient.

The surgery was performed by the primary author with the patient supine initially for placement of right external ventricular drainage catheter (EVD) using standard landmarks at the right Kocher’s point. Following EVD placement the patient was positioned prone and underwent a 4 cm × 3 cm suboccipital decompressive craniectomy with opening of the foramen magnum. A left cerebellar biopsy was obtained from infarcted tissue including an arterial and venous vessel and 1 cm × 1 cm section of parenchyma and dura. Pathology revealed a single vessel, presumably a vein, with a small organizing thrombus adjacent to a focally proliferative intima with intimal neutrophils, without evidence of arterial vasculitis. Focal scattered neutrophils within the molecular layer of the cerebellar tissue were also noted. (Fig. 3).

On post operative day (POD) 1 patient had ICP’s in the high 30s that were controlled with mannitol, hypertonic saline and EVD drainage. Mannitol was started by the neurocritical care service and was discontinued by the neurosurgical service as there is no evidence of its benefit in a patient with external ventricular drainage. The EVD was weaned and discontinued on POD 6. Patient began to follow commands on the right side and remained hemi paretic on the left side. Patient respiratory status was improved and transferred to a rehabilitation facility and neurologically stable in follow up.

3. Discussion

Much of the pathophysiology pertaining to SARS-Cov-2 infection is not well understood. There has been some resemblance to disease caused by SARS-Cov-2 to SARS-Cov and MERS; with direct infection of type-II pneumocytes, via the ACE-2 receptor binding domain during the initial phase of illness [3–5]. The pathogenesis also involves immune dysregulation, which has been noted in severely ill patients with SARS-Cov-2 infection [6–8]. Two distinct syndromes have been noted in patients with COVID-19; immune dysregulation and macrophage activation syndrome [8]. An increase in inflammatory cytokines, has been noted in both, with majority of patients noted to have elevated interleukin-6 levels [8]. Levels of Interleukin-6 have also been shown to correlate with increased severity of disease, disease progression and...
Arterial thrombosis and associated intracerebral stroke frequency has been noted as the current COVID-19 pandemic continues [2,25,26,28]. Previous descriptions of stroke phenomenon requiring either neuroendovascular intervention or formal surgical intervention have been reported, acute ischemic events involving peripheral arterial

**Fig. 2. Noncontrast Head CT Time Course.** A. Hospital Day 5. Noncontrast head CT at time of stroke alert, note no hypodensity, no hydrocephalus and no mass effect on fourth ventricle. B. CT Angiogram head at time of stroke alert, note vertebral artery occlusion (arrows). C. Hospital Day 6. CT head non-contrast shows left cerebellar infarct with effacement of the CP angle cistern and left-to-right midline shift without hydrocephalus, fourth ventricle remains patent. D. Hospital Day 7. CT head non-contrast shows evolving left cerebellar stroke with increasing mass effect on the fourth ventricle without hydrocephalus. E. Hospital Day 9. CT head non-contrast shows left cerebellar infarct with significant mass effect on the fourth ventricle and paramensecephalic cistern. No hydrocephalus.

**Fig. 3. H&E permanent section of left cerebellum brain biopsy, note histology leptomeningeal vein with neutrophilic infiltrates (arrows) in the blood vessel wall. The asterisk denotes a fibrin plug in the lumen of the vein. The scale bar equals 50 µm.**

poor prognosis in addition to certain other biomarkers; these include elevated ferritin, elevated white blood cell count, lymphopenia, and elevated platelet count [9,10].

Apart from biomarkers of inflammation, co-morbidities including diabetes and hypertension, have also been shown to be risk factors for severe disease [11,12]. This was also noted in our patient, who was a diabetic and had hypertension increasing his risk for progression to severe disease. He was noted to have lymphopenia, elevated CRP, ferritin, and was later shown to have increased interleukin-6 levels, showing immune dysregulation. Moreover, our patient also tested positive for anti-cardiolipin IgM and Beta 2 GPI IgA antibodies, which is concerning for anti-phospholipid antibody syndrome; which has also been described in two other diabetic patients with stroke one of which also had significant coagulopathy similar to our patient who developed sudden increase in D-dimer (> 20.0 ng per milliliter) and elevated PT, PTT and low fibrinogen levels (158 mg per deciliter), interestingly with a normal platelet count on day 6 of admission [13]. Infection accounts for the cause of 8–11% of cases of cerebral venous thrombosis [14]. Our patient had radiographic evidence of arterial thrombosis and pathological evidence of venous thrombosis. Larger studies will be helpful to examine the impact of diabetes in COVID-19 patients as a risk factor for development of anti-phospholipid antibodies, coagulopathy and stroke.

Interestingly, severity of COVID-19 has been shown to correlate with risk of coagulopathy and stroke in Caucasian patients, and in general, ethnicity has been shown have a major effect in the risk of thrombosis with African Americans at higher risk than Caucasians or Chinese [15]. Given interleukin-6 levels have also been shown to be elevated in patients critically ill with COVID-19, it would be interesting to know if there is a correlation between risk of stroke and coagulopathy with increased levels of interleukin-6 [8]. It could be hypothesized that immune dysregulation can predispose patients to anti-phospholipid antibody syndrome or development of clinically significant coagulopathy, and hence, increase their risk of stroke. However, whether this effect holds true in the presence of co-morbidities could be better assessed in larger clinical trials.

Our patient was identified to be in a state of immune dysregulation, given increased CRP, ferritin, and interleukin-6 levels, and hence one dose of off-label Tocilizumab was given in an attempt rescue immune dysregulation by SARS-CoV-2. Tocilizumab is an Interleukin-6 receptor antagonist, shown to be beneficial in treatment of patients with severe disease from SARS-CoV-2 in smaller studies, however, larger studies are needed and are underway to examine the impact on morbidity and mortality [16,17]. Tocilizumab did not demonstrate increased risk of hypercoagulability, thrombosis or drug interaction that led to increased coagulability [18]. Some benefit was noted in our patient, with improving markers of inflammation, and respiratory status, however, the clinical picture was complicated by severity of stroke and associated edema with impending herniation.

The patient had been on supportive care prior to his stroke and was not given any medication that had side effects or drug interactions that would increase his risk of thrombosis and stroke.

Currently, treatment modalities for SARS-CoV-2 infection are limited, with need for larger studies, and randomized trials showing a benefit in outcomes and mortality. Recently, the FDA approved use of convalescent plasma for critically ill patients with COVID-19, and more recently, emergency use authorization of use of Remdesivir to allow for distribution in the United States for treatment of severe disease. At the time of this writing, Remdesivir is only available to a few sites in United States, with majority with access for compassionate use in pregnant women and children [19].

Convalescent plasma has been studied in infections with SARS-CoV and MERS, and it is hypothesized it may improve mortality in patients infected with SARS-CoV-2, with good experience noted in smaller studies [20–22]. Several clinical trials are ongoing to examine the effect of convalescent plasma, including one at our institution. It would be interesting to know if early administration of convalescent plasma is beneficial is prevention of cytokine cascade, increased levels of immunoregulatory cytokines, and immune dysregulation. This might reduce the impending severity of disease, and possibly mortality from infection.

Arterial thrombosis and associated intracerebral stroke frequency has been noted as the current COVID-19 pandemic continues [2,25,26,28]. Previous descriptions of stroke phenomenon requiring either neuroendovascular intervention or formal surgical intervention have been reported, acute ischemic events involving peripheral arterial
vessels with limb ischemia have also been noted [2,22]. Hypotheses as to the pathophysiologic causes have been discussed and a virus related state of hypercoagulability may be the direct result in select groups of individuals [2,23]. Unfortunately the systemic cause of hypercoagulability has not been pinpointed and trends associated with d-dimer elevations during the course of arterial vessel thrombosis both in our ability has not been pinpointed and trends associated with d-dimer individuals [2,23]. Unfortunately the systemic cause of hypercoagulability may be the direct result in select groups of vessels with limb ischemia have also been noted[2,22]. Hypotheses as to the pathophysiologic causes have been discussed and a virus related state of hypercoagulability may be the direct result in select groups of individuals [2,23]. Unfortunately the systemic cause of hypercoagulability has not been pinpointed and trends associated with d-dimer elevations during the course of arterial vessel thrombosis both in our ability has not been pinpointed and trends associated with d-dimer individuals. COVID-19 complicated with cerebral and large vessel vasculitis is of growing concern as per clinicaltrials.gov that are looking at the efficacy of dexamethasone in COVID-19 patients. Corticosteroids as a treatment for cerebral vasculitis is well documented [29]. It would be interesting to see if these trials show lower incidence of strokes in their cohorts. COVID-19 complicated with cerebral and large vessel vasculitis and its treatment will require a need for randomized clinical trials showing benefit in outcomes and mortality.

The infectious process of COVID-19 remains a systemic event with pathophysiologic evidence of vasculitis involving the lungs, venous and arterial systems. As the disease process is further defined, it will be imperative that new diagnostic strategies are developed along with tracking of individual coagulopathy. Early neurosurgical consultations may have to be considered when patients present with neurologic changes or suspected intracranial ischemic phenomenon. As case numbers and data are compiled, trends may be noted thus simplifying treatment modalities necessary for thrombo-embolic complications.

4. Conclusion

This is a report of a patient with COVID-19 immune dysregulation who developed an acute cerebellar ischemic stroke secondary to vertebral artery thrombosis. A biopsy showed venous phlebitis with neutrophilic infiltration of the vessel wall. The patient had a large vessel occlusion from presumed arteritis with intracranial evidence of venous involvement indicating a possible pathophysiologic mechanism for incidence of thrombosis and stroke in COVID-19 patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inat.2020.100850.

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