

## Rapid Evolution of Cerebral Edema in an Elderly with Ischemic Stroke and COVID-19: The Possible Role of Cytokine Storm

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### Abstract

Varied neurological manifestations have been recognized in patients with the novel coronavirus disease 2019 (COVID-19) including cerebral vascular events. Here we reported a 78-year old patient with COVID-19 who suffering from right middle cerebral artery ischemic stroke rapidly developed cytotoxic edema with significantly elevated inflammatory biomarkers. Presumably what has been called cytokine storm resulted from SARS-CoV-2 infection likely played a role in this patient's rapid both radiographic and clinical devastating outcome on day-2 after ischemic stroke. Timely lifesaving intervention should be considered in stroke patients with COVID-19 in the setting of cytokine storm.

### Keywords

COVID-19, Acute ischemic stroke, Cerebral edema, Inflammation

### Introduction

In December 2019, an outbreak of a pneumonia-like disease was reported in Wuhan, China, caused by the 2019-novel coronavirus. Due to clinical symptoms of the 2019-novel coronavirus are similar as that of severe acute respiratory syndrome coronavirus (SARS-CoV) of 2003 and both share the same receptor of angiotensin converting enzyme 2, this virus was therefore named SARS-CoV-2. The World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) as a pandemic on March 11, 2020 and 8.9 million cases and 467,320 deaths worldwide have been reported as of June 21, 2020.

Patients infected with SARS CoV-2 most commonly manifest respiratory symptoms. However, there are reports of varied presentations including neurological symptoms that could precede respiratory symptoms and fever. Data regarding the neurological manifestations of the coronavirus is sparse and has been limited to case reports and correspondence. Recently, an observational study [1] from Wuhan, China, reported 2.8% (6 out of 214) of acute cerebrovascular disease in patients with COVID-19. Additionally, case reports [2] have also linked coagulopathy and strokes with COVID-19. We present a case of a large middle cerebral artery (MCA) territory stroke with rapid progression of cerebral edema possibly due to SARS-CoV-2 induced cytokine storm.

### Case Presentation

A 78-year-old left-handed woman presented with right middle cerebral artery syndrome along with global aphasia and last known well 18 hours prior. Her past medical history was significant for new onset atrial fibrillation not on

anticoagulation and colon cancer resected 10-year ago without recurrence per following colonoscopies. Her NIH stroke scale was 26, but she was not a candidate for tissue plasminogen activator (tPA) because she was out of the therapeutic window. No mechanical thrombectomy took place due to noncontrast head computed tomography (CT) showing right middle cerebral artery (MCA) territory hypodensity, Alberta stroke program CT score (ASPECTS) 5, CT angiogram revealed proximal right middle cerebral artery occlusion, and CT perfusion (CTP) showing large stroke core 80mL, penumbra 105 and mismatch ratio 1.3 **Figure 1 (A-B)**. The patient was admitted to stroke service for continued clinical monitoring and further workup.

The first night of admission the patient was noted to have apneic episodes, oxygen desaturation requiring 3L nasal cannula, tachycardia, tachypnea and fever of 38.2 °C. Chest x-ray (**Figure 1C**) showed findings of multifocal pneumonia and the patient tested positive for COVID-19 on real-time reverse-transcription polymerase chain reaction (PCR) analysis of throat swab specimen. Repeated head CT at 36 hours after presentation showed evolution of right MCA infarction, mass effect and midline shift of 13 mm (**Figure 1D**). Laboratory work revealed elevated inflammatory markers (**Figure 1E**). Additionally, D-Dimer (normal range 0-500 ng/

mL) was continuously elevated from 3,310 on day-1 to 3,440 ng/mL on day-2 of admission; it then dropped to 2,080 ng/mL on day-3, but jumped to above 4,000 ng/mL on day-5 of admission.

The patient was started on hyperosmolar therapy, required mechanical ventilation and no decompressive hemicraniectomy took place per decision of neurosurgery and patient's decision maker. Intracerebral pressure (ICP) continued to rise despite aggressive medical therapy, and the patient's family made her comfort care, respecting her wishes.

## Discussion

The most feared complications of malignant MCA stroke are cerebral edema leading to increased ICP and brain herniation. Initial phase of cytotoxic edema (which is due to failure of ATP-dependent ion transport) evolves over minutes to hours after ischemic stroke, while subsequently vasogenic edema (which is mainly due to endothelial dysfunction of the capillaries, resulting in breakdown of the blood-brain barrier) occurs over hours to days from onset of ischemic stroke [3]. It is well documented in the literature that cerebral edema usually peaks between 3-5 days after infarction [3, 4]. There are no objective predictive measures that assess the patient's likelihood to develop these feared complications. Factors that clinicians consider when contemplating specific management, both medical and surgical, include the age of the patient and degree of cortical atrophy.

In our patient, even though both her age and degree of cortical atrophy were significant, they were not good predictors of her clinical course. This disconnect lead us to question whether excessive inflammatory response "cytokine storm" is seen in response to SARS-CoV-2 infection [5, 6], which likely played role in the patient's rapid both radiographic and clinical outcome. **Figure 1E** shows the trend of inflammatory markers in our patient, which demonstrated rapid inflammatory response right after acute ischemic stroke in the setting of SARS-CoV-2 infection. These inflammatory biomarkers measured in our reported case are based on previous studies [7-9] indicating they are associated with the inflammatory process as well as the disease severity.

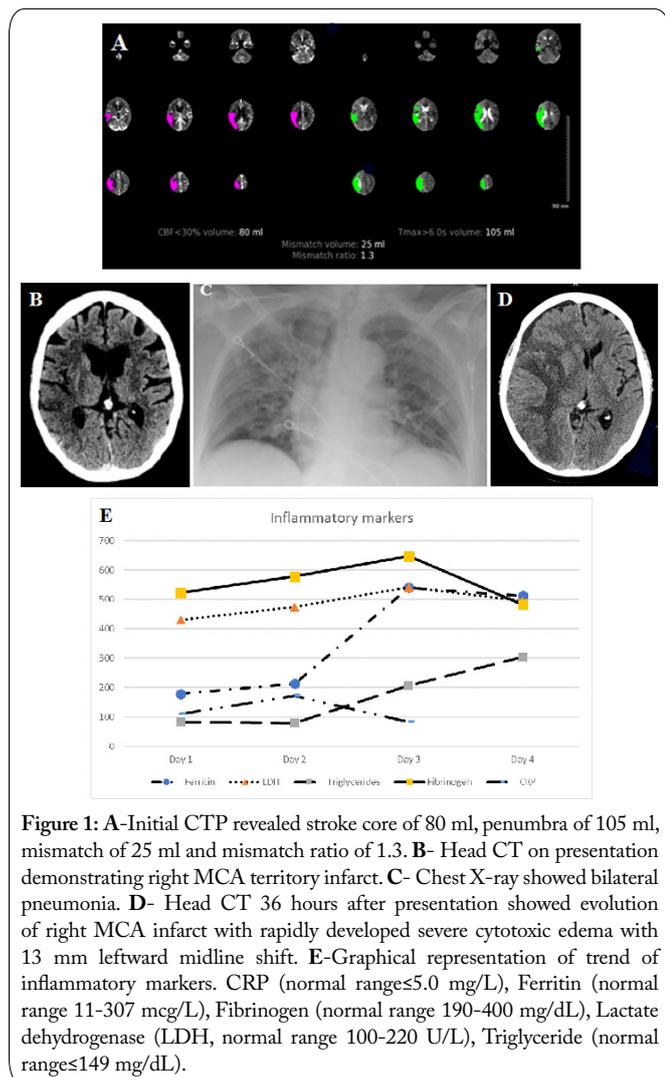
So far, there have been reports of large vessel occlusions and stroke in young in COVID-19 patients [10]. As the number of COVID-19 cases continues to rise, along with the awareness of association of stroke with COVID-19, we should keep in mind that there may be a hastened natural history of malignant MCA stroke which may help in early decision-making regarding lifesaving interventions.

## Authors Contribution

Authors FR and HP are contributed equally to the study.

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**Figure 1:** A-Initial CTP revealed stroke core of 80 ml, penumbra of 105 ml, mismatch of 25 ml and mismatch ratio of 1.3. B- Head CT on presentation demonstrating right MCA territory infarct. C- Chest X-ray showed bilateral pneumonia. D- Head CT 36 hours after presentation showed evolution of right MCA infarct with rapidly developed severe cytotoxic edema with 13 mm leftward midline shift. E-Graphical representation of trend of inflammatory markers. CRP (normal range≤5.0 mg/L), Ferritin (normal range 11-307 mcg/L), Fibrinogen (normal range 190-400 mg/dL), Lactate dehydrogenase (LDH, normal range 100-220 U/L), Triglyceride (normal range≤149 mg/dL).

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