

CASE REPORT



Hemorrhagic infarctive stroke in COVID-19 patients: report of two cases and review of the literature

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ABSTRACT

There is growing evidence in support of ischemic stroke as a manifestation of COVID-19 infection. However, hemorrhagic transformation of ischemic stroke is rare. We present two cases of hemorrhagic infarction as presenting features in COVID-19 patients who did not have traditional cardiovascular risk factors for ischemic or hemorrhagic stroke. While the hemorrhagic infarct was from a large artery in one of the patients, the other patient had a small artery related hemorrhagic infarct. We highlighted the possible underlining mechanisms from the literature and the implication of hemorrhagic infarct for routine anticoagulant therapy in patients with COVID-19 related ischemic stroke.

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1. Introduction

Although the most common presentation of COVID-19 infection is with respiratory manifestations, there are growing reports of associated neurological manifestations in people with COVID-19 infection[1]. Association between COVID-19 and stroke in people without the traditional cardiovascular risk factors, occasionally with minimal respiratory features, is on the increase[1]. Despite this increase in the incidence of stroke, there is some uncertainty as to whether COVID-19 is associated with a higher risk of infarctive stroke than would be expected from a viral respiratory infection. In a recent study, Alexander et al. showed that COVID-19 who visited the ER or were hospitalized had a higher rate of infarctive stroke in comparison with a cohort of patients in the same setting with influenza[2]. There are reports that suggest that COVID-19 may result in a hypercoagulable state and hence, thrombotic complications [2,3]. While the pathogenesis of hemorrhagic COVID-19-related stroke is still obscure[4], hypercoagulable state, vasculitis, and cardiomyopathy have been hypothesized as the main mechanisms responsible for the occurrence of infarctive strokes in COVID-19 infection [5,6]. Recent publications from various countries have raised the possibility of a higher risk of infarctive stroke in patients with COVID-19 infection [5,7]. A retrospective data from the study of COVID-19 patients in Wuhan, China, revealed that the incidence of stroke among hospitalized COVID-19 patients was about 5%[7]. Therefore, infarctive stroke in COVID-19 cannot be considered

a total rarity. However, there is a dearth of reports on hemorrhagic transformation after brain ischemia in COVID-19 patients. We report two cases of COVID-19-related HI stroke in patients who presented to our health care facility in Bisha, Saudi Arabia.

2. Case report

2.1. Patient 1

A 59-year-old man presented, 5 days after COVID-19 symptoms of fever cough, breathlessness, muscle pain and poor appetite, with a 4-hour history of sudden onset right side incoordination, weakness, facial deviation, and altered level of consciousness. He was neither hypertensive nor diabetic. He had no history of previous transient ischemic attack or stroke and there was no history suggestive of background cardiovascular risk factors. No family history of hypertension, diabetes, heart diseases or stroke.

He did not take antiplatelet or anticoagulation prior to presentation. Examination revealed an acutely ill-looking and febrile (38° c) man with Glasgow Coma Score (GCS) of 13/15, subtle neck stiffness but absent Kernigs and Brudzisky signs. He had right upper motor facial and abducent nerves palsy. His pupils were 3 mm bilaterally and reactive appropriately to light. Motor system examination revealed right flaccid hemiplegia. His pulse rate was 96/min (normal volume and rhythm), blood pressure 140/90 mm Hg and heart sounds were normal.

The essential findings on his chest examination were tachypnea (24breath/min) and a few coarse

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crepitations bilaterally. His SpO₂ at presentation was 90% on an oxygen mask. His CXR showed bilateral infiltrates, COVID-19 PCR test was positive, Brain CT revealed an extensive left acute fronto-parietal subcortical infarct with hemorrhagic transformation and ventricular extension (Figure 1).

His COVID-19 infection severity was considered severe[8]. His Lipid profile, platelet count and INR were all within normal limits. He was immediately transferred to ICU where he received treatment for COVID-19 infection and stroke as per Saudi Arabia Ministry of health COVID-19 treatment guideline (Hydroxychloroquine, Dexamethasone, Remdesivir, Antibiotics among others)[8]. Later, his SpO₂ declined to 70% and the mechanical ventilator was instituted. A repeat PCR test was negative on day 20th of admission. About 22 days of presentation his level of consciousness deteriorated (GCS = 3/15) and he died on the same day.

2.2. Patient 2

A 51-year-old, COVID-19 positive (by PCR) patient was referred to our center from a neighboring general hospital with a two-day history of sudden onset left side limb and facial weakness. He was neither hypertensive nor diabetic. There was no history of previous

transient ischemic attack or stroke and there was no history suggestive of background cardiovascular risk factors. He had no family history of hypertension, diabetes, heart diseases or stroke. There was no history of prior antiplatelet or anticoagulation ingestion. Examination revealed an acutely ill-looking and afebrile (37° c) man with an altered level of consciousness (GCS = 14/15). He had a left upper motor facial. His pupils were 3 mm bilaterally and reactive appropriately to light. Power in his left upper and lower limbs was 3/5. His pulse rate was 80/min (normal volume and rhythm), blood pressure 130/86 mm Hg, and normal heart sounds. No abnormality was detected on his chest examination. His SpO₂ at presentation was 98%. His CXR showed minimal bilateral infiltrates. His COVID-19 infection was considered mild to moderate[8]. His brain CT (Figure 2) showed a small-sized infarct with a hemorrhagic core in the right basal ganglia. His Lipid profile, platelet count and INR were all within normal limits. Similar to the former patient, he was managed in ICU where he received treatment for COVID-19 infection and stroke as per Saudi Arabia Ministry of health COVID-19 treatment guideline (Hydroxychloroquine and others with the exception of Remdesivir). The patient's clinical condition improved significantly and his second PCR test was negative. He was alive as at the time of this report. Table 1 shows the baseline clinical,

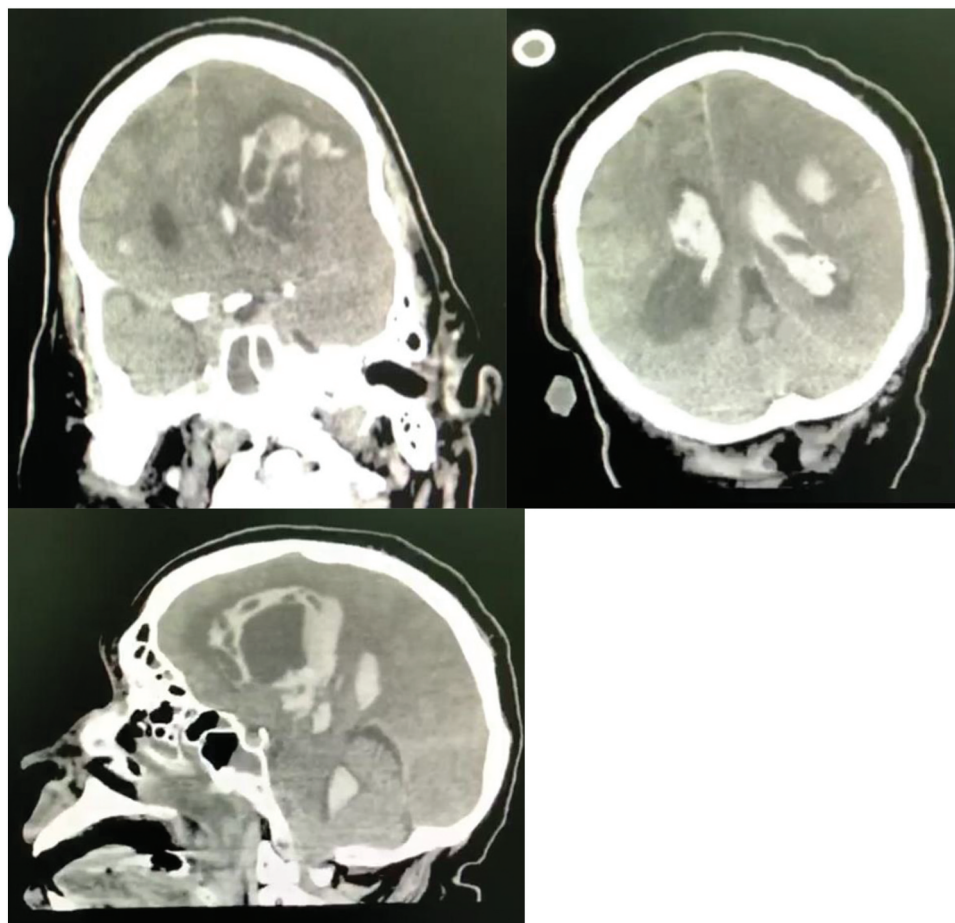


Figure 1. Shows a right hemispheric massive hemorrhagic infarct with ventricular extension in patient 1.



Figure 2. Shows a small-sized right hemispheric infarct with a pin-point hemorrhagic transformation.

Table 1. Showed the baseline clinical, laboratory and radiological characteristics of the patients.

Demographic, laboratory, and radiological characteristics	Patient 1	Patient 2
Age	59	51
Gender	Male	Male
PCO ₂ at presentation (%)	90	98
Severity of COVID-19 at presentation	Severe	Mild to moderate
GCS (/15)	13	14
BP (mmHg)	140/90	130/86
CXR finding	Bilateral lung infiltrates	Minimal lung infiltrates
Random glucose (mg/dl)	Normal	Normal
LFT	Normal	Normal
Serum creatinine	Normal	Normal
Serum Na	Normal	Normal
Serum K	Normal	Normal
Serum HCO ₃	Normal	Normal
Lipid profile	Normal	Normal
ECG	Normal	Normal
Brain CT	Extensive left acute fronto-parietal subcortical infarct with hemorrhagic transformation and ventricular extension	A small-sized infarct with hemorrhagic core in the right basal ganglia

laboratory and radiological characteristics of the patients

3. Discussion

To date, few studies have reported cerebral infarction in COVID-19 patients, fewer studies have reported

hemorrhagic stroke in the COVID-19 population and much fewer have documented hemorrhagic infarction in them. A panel of the World Stroke Organization, in a review, reported that the risk of COVID-19-related ischemic stroke is about 5%[9]. However, hemorrhagic strokes in COVID-19 patients are much less common than ischemic strokes and only a few cases have been reported thus far [10–12]. We report two cases of COVID-19 related cerebral hemorrhagic infarcts in two middle-aged men without the traditional risk factors for infarctive or hemorrhagic stroke. One of them had a hemorrhagic transformation of an extensive cerebral infarction and the other had a hemorrhagic transformation of a relatively small cerebral infarction.

As the COVID-19 pandemic progresses, there has been a growing number of case series and case reports describing a wide array of COVID-19 related neurological manifestations. The neurological manifestation reported so far, to list but a few, included encephalopathy, encephalitis, Guillain Barre Syndrome, and anosmia [7,13]. Stroke is yet another emerging associated condition of COVID-19 infection. Of the few publications highlighting stroke in the setting of COVID-19, the frequency of stroke in COVID-19 varies. In China, among 214 hospitalized COVID-19 patients, 3% developed stroke [7]. In France, of the 13 patients with COVID-19 infection that had brain MRI, about 23% had evidence of

ischemic stroke [14] while in the US, 0.9% of 3556 COVID-19 patients had an ischemic stroke [15].

Three principal mechanisms that appear to underlie the occurrence of COVID-19-related ischemic stroke [5,6]. These mechanisms are a hypercoagulable state, vasculitis, and cardiomyopathy. Other pathophysiologic mechanisms that have been hypothesized for COVID-19-related ischemic stroke include hypotension and inadequate cerebral perfusion; relative hypertension leading to posterior reversible encephalopathy syndrome; hyper-inflammatory state; and septic embolization in those with superimposed bacterial infection[15]. Clinically significant coagulopathy with antiphospholipid antibodies presence has also been described in COVID-19 related multiple cerebral infarcts in another study[3].

Unlike in ischemic stroke, the pathogenesis of hemorrhagic strokes in patients with COVID-19 is still obscure. Nevertheless, there are speculations that firstly, because of the strong affinity of the SARS-CoV-2 for angiotensin-converting enzyme 2 (ACE2) receptors, which are present on many cell types including endothelial and arterial smooth muscle cells in the brain, possibly leads to the destruction of the cerebral arteries with attendant vessel wall rupture[16]. Secondly, the cytokine storm (hypercytokinemia) that occurs in the setting of COVID-19 infection could be the drive for hemorrhagic strokes in the disease[4]. In support of this was the report of acute necrotizing encephalopathy and late parenchymal brain hemorrhages in a COVID-19 patient[11].

To date, a few hemorrhagic transformations of infarctive strokes have been documented in COVID-19 patients [10,17]. The two cases we presented suggest that COVID-19, though capable of manifesting as ischemic stroke, could also present with secondary hemorrhagic transformation. Additionally, as demonstrated in the two cases, these can occur as a large vessel disease, as exemplified by the first case, or a small vessel occlusion, as demonstrated in the second case, with attendant hemorrhagic transformation. It is possible that endothelial damage with or without a consumption coagulopathy culminate in hemorrhagic infarction in such patients with COVID-19 infection[17].

The limited clinical data about the virus's behavior to date, particularly regarding neurologic manifestations, suggest that caregivers should be aware of the possibility of hemorrhagic infarction in patients with COVID-19-related ischemic stroke. This has a significant implication given the pathophysiologically driven tendency to routinely use anticoagulant in patients with COVID-19 and ischemic stroke. Therefore, caution should be exercised before such anticoagulant or antiplatelet is administered in the setting of COVID-19 related ischemic stroke.

It is, however, worthy of note that the cases reported here are too few to reach a flawless conclusion on the relationship between COVID-19 and hemorrhagic infarcts. Therefore, further experimental and epidemiological studies are needed to find out the exact relationship between them.

4. Conclusion

We report two cases of COVID-19 related cerebral hemorrhagic infarct in the absence of traditional risk factors for cerebral ischemia or hemorrhage.

Disclosure statement

All the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this case report.

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