Spontaneous Non-Aneurysmal Subarachnoid Hemorrhage as Initial Presentation of COVID-19: A Case Report

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Abstract

Introduction: Cerebrovascular events have been reported in patients with COVID-19, with ischemic being more common than hemorrhagic strokes. We present an asymptomatic elderly with spontaneous non-aneurysmal subarachnoid hemorrhage who was subsequently diagnosed with COVID-19 critical pneumonia. Spontaneous non-aneurysmal subarachnoid hemorrhage as an initial manifestation of SARS-CoV-2 infection is yet to be documented.

Objectives: This report presents a 75-year-old female with spontaneous non-aneurysmal subarachnoid hemorrhage as initial finding in a background of SARS-CoV-2 infection. We reviewed related literatures that will give insights on the dilemmas encountered in determining the association of spontaneous subarachnoid hemorrhage as a manifestation of COVID-19.

Case presentation: A 75-year-old female was brought to our institution after a presyncopal attack. Cranial neuroimaging showed non-aneurysmal subarachnoid hemorrhage. While hospitalized, she developed fever and dyspnea, subsequently diagnosed COVID-19, developed critical pneumonia and died of pulmonary complications.

Conclusion: This is a possible case of an undetected SARS-CoV-2 infection in an otherwise asymptomatic patient who initially presented with a spontaneous subarachnoid hemorrhage and later progressed to critical pneumonia leading to demise. Factors outside the context of COVID-19 were reviewed with limited literatures. Further epidemiological and clinical studies are warranted to clearly establish spontaneous subarachnoid hemorrhage as an initial manifestation of COVID-19.

Keywords: COVID-19 • Hemorrhage • Stroke • Infection

Introduction

Nontraumatic spontaneous Subarachnoid Hemorrhage (SAH) is a neurologic emergency comprising 1-7% of all stroke events with an overall 28-day post-ictal case fatality rate of 41.7% [1]. It is commonly caused by ruptured cerebral aneurysms in 80%-85% of cases [2]. Close to half of survivors are left with long term neurological and cognitive impairments. Older patients with hypertension are at higher risk of developing aneurysmal SAH, indicating the association of older age and hypertension with cerebrovascular disease and aneurysm formation and rupture, respectively. Studies have demonstrated that female gender is a known risk factor for aneurysmal SAH but with lower incidence for non-aneurysmal SAH [1,2]. Symptoms typically evolve from sudden headache to loss of consciousness, development of neurologic deficits and/or ensuing changes in sensorium.

Though the major clinical manifestations of COVID-19 are secondary to pulmonary complications, acute neurologic complications were reported. Stroke is an uncommon neurological complication of SARS-CoV-2 infection, comprising only 5.9% of cases [3,4]. Moreover, a study including 214 patients across three hospitals in Wuhan, China reported stroke to account only for 2.8% of total cases of neurologic manifestation in patients with COVID-19 infection. Dizziness (16.8%), headache (13.1%) and impaired consciousness (7.5%) comprised the majority of clinical characteristics of hospitalized patients with neurologic manifestation in the included study population [5].

Cerebrovascular events have been reported in patients with COVID-19, with ischemic strokes being more common (incidence of 0.4 to 2.7% among hospitalized patients) than hemorrhagic strokes (incidence of 0.2 to 0.9% among hospitalized patients). The risk for developing stroke among those with COVID-19 varies between <1% for those with mild illness to 6% among those admitted for intensive care. It occurs most commonly 1 to 3 weeks after the onset of COVID-19 symptoms. Stroke as initial symptom leading to hospitalization is reported only in few instances [6,7].

There are insubstantial reports of nontraumatic subarachnoid hemorrhage developing in hospitalized patients with severe COVID-19. Intracerebral hemorrhage and SAH are both associated with poorer prognosis in terms of in-hospital morbidity and mortality [8]; the causal relationship and mechanism between SAH and COVID-19 has yet to be fully established to date. Non-aneurysmal SAH in an otherwise asymptomatic, healthy person who was later on diagnosed to have COVID-19 and developed critical pneumonia has not yet been documented.

This study aims to elaborate on the question whether spontaneous SAH could be an initial neurologic manifestation of COVID-19 and not just a complication of SARS-CoV-2 infection.

Case Synopsis

A 75-year-old female was brought to our institution due to transient altered consciousness. Fifteen minutes prior to emergency department consultation, she experienced dimming of vision associated with confusion, dizziness, and generalized body weakness. The symptoms spontaneously resolved after several minutes. There were no other symptoms noted prior to and during this event. She denied any head trauma. Patient was brought to our institution for evaluation.

She was hypertensive, maintained on irbesartan, carvedilol and aspirin, with a usual blood pressure of 110/80. She had no prior history of hospitalization nor surgery. She denied any history of smoking, alcoholism nor illicit drug use. There was no history of cognitive, behavioral or any related neurologic symptoms prior to the event. Exposure to possible COVID-related cases was limited to an occasion of travel more than 2 weeks prior to development of symptoms.

At the emergency department, patient was received ambulatory, coherent, with no subjective neurological complaint. Physical examination revealed

hypotension at 90/60 mmHg, hyperthermia at 38.0°C. Her head was atraumatic with an unremarkable cardiopulmonary evaluation. Neurological examination was likewise normal. Plain cranial CT scan showed minimal subarachnoid hemorrhage at biparietal lobes (Figure 1) and right occipital region. Chest x-ray revealed no evidence of active pneumonic infiltrates (Figure 2). Assay of inflammatory markers was elevated with a D-dimer of 1,456.94 ng/ml (Normal value: 0-500 ng/ml), serum ferritin of 610.89 ng/ml (Normal value: 20-250 ng/ml), procalcitonin of 0.23 ng/ml (Normal value: <0.5 ng/ml), lactate dehydrogenase of 361 u/L (Normal value: 313-618 u/L), C-reactive protein of 175.15 mg/L (Normal value: 0-10 mg/L). Coagulation tests (platelet count, prothrombin time and activated partial thromboplastin time) were within normal limits. Patient was admitted for further evaluation and monitoring.

At first hospital day, tranexamic acid infusion, nimodipine, levetiracetam, paracetamol and citicoline were administered. Patient was maintained on complete bed rest. Cranial CT-angiography done at day 2 postictus showed no vascular abnormalities and an interval decrease in the amount of the multifocal intracerebral and subarachnoid hemorrhage at right (Figures 3 and 4).

On the third hospital day, intermittent fever was noted. She experienced episodic dyspnea associated with desaturation as low as 88%. Chest radiograph revealed interval development of scattered hazy densities in both lung fields (Figure 5). Arterial blood gas study showed compensated respiratory alkalosis with hypoxemia. Her RT-PCR for SARS-CoV-2 revealed a positive result hence was started on ceftriaxone, remdesivir and dexamethasone. Due to persistent desaturation despite oxygen support, she was hooked to non-rebreather face mask. Her neurological examination remained unremarkable.

On the fifth hospital day showed further worsening of oxygen desaturation.

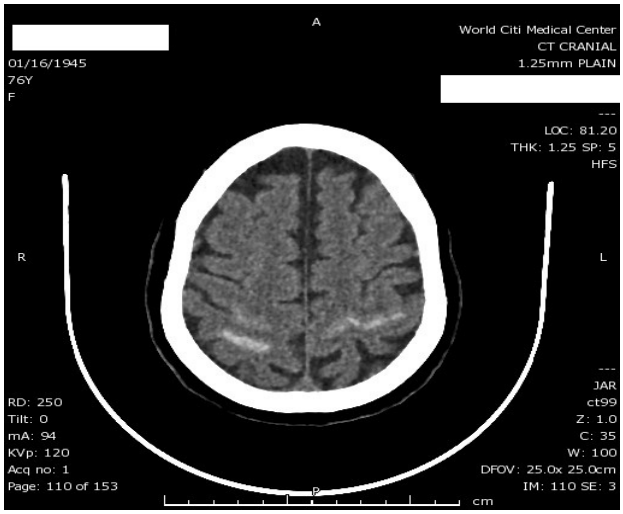

Figure 1. Plain cranial CT scan upon initial consult showing bilateral lobar haemorrhage.

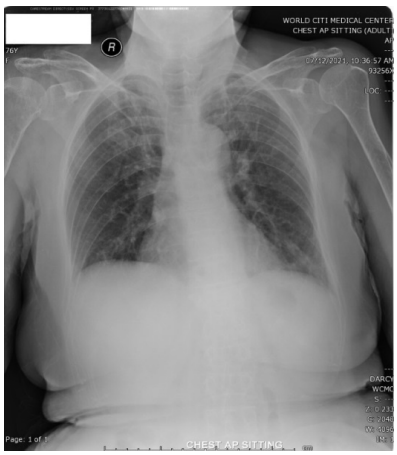

Figure 2. Chest x-ray upon initial consult.

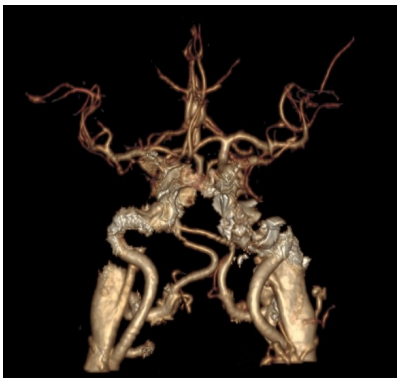

Figure 3. CT angiography of patient done at hospital day 2 showing no vascular abnormalities.

Figure 4. CT angiography of patient done at hospital day 2 showing no vascular abnormalities.

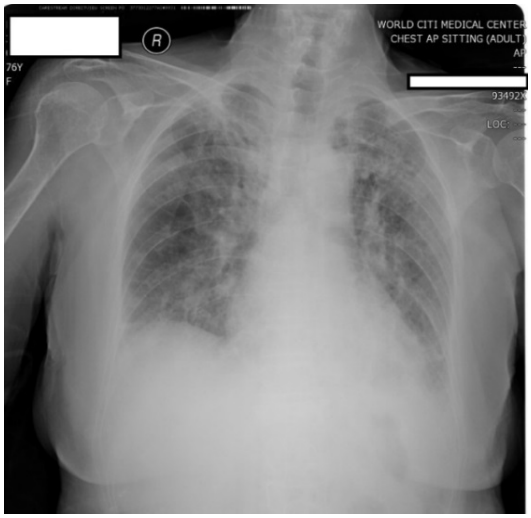

Figure 5. Chest X-ray at day 5 of hospitalization showing progression of bilateral hazy infiltrates.

Serial arterial blood gas studies showed inadequate oxygenation. Oxygen support was revised to high-flow nasal cannula.

During the interim, there was noted progressive worsening of respiratory symptoms and overall clinical status. Physical examination was consistent with progressive pneumonia as evident by persistent tachypnea, decreasing oxygen saturation and worsening coarse crackles noted on both lower lung fields. Patient was eventually intubated due to impending respiratory failure. Serial chest radiograph showed progression of bilateral hazy infiltrates (Figure 6). Antibiotic revision and adjustment of supportive medications were done. At hospital day 19, she developed Acute Respiratory Distress Syndrome (ARDS) and eventually expired. The case was signed out as ARDS secondary to COVID-19 infection with critical pneumonia and non-traumatic subarachnoid hemorrhage.

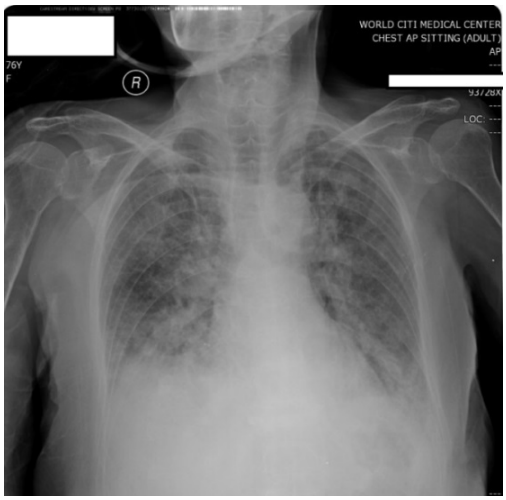

Figure 6. Chest X-ray at day 8 of hospitalization showing further progression of bilateral hazy infiltrates.

Results and Discussion

Respiratory symptoms are the more commonly reviewed presentation at our emergency department in terms of triaging cases that should be labeled under suspected COVID-19 and non-COVID-19 related cases. With evolving knowledge about the SARS-CoV-2 virus, we aim to expand our understanding of its behavior that may be beneficial in early detection, management and surveillance of COVID-19 cases.

Broad range of neurologic manifestations of COVID-19 has been reported, with incidence of each symptoms varying across different studies. In a study by Chou et al. including 3744 patients, 80% of those hospitalized for COVID-19 infection initially self-reported a variety of neurologic symptoms, with headache (37%) and anosmia or ageusia (26%) as the 3 most common [9]. Acute encephalopathy is the most common verified neurological sign in the same study. Other neurologic manifestations include stroke, meningoencephalitis, schizophrenia-like illness, Guillain-Barre syndrome, and neuromuscular disorders among others, with dizziness being the most common (up to 17%) in a study done by Desai, et al. [10]. Infection with SARS-CoV-2 increases the risk for strokes, with ischemic events more notably observed than both intracerebral hemorrhage and subarachnoid hemorrhage [7,11]. Majority of reported non-traumatic SAH in severe COVID-19 demonstrated no evidence of aneurysms on imaging [12,13].

While no study has yet to elucidate the exact pathophysiology on how COVID-19 raises the risk for intracranial hemorrhagic events, several mechanisms has been proposed including pro-inflammatory states promoting vascular endothelial injuries via increased collagen breakdown, leading to rupture of blood vessels; increased permeability of blood-brain barrier [12]; secondary haemorrhages from micro thromboses and concomitant anticoagulation therapy [13]. Spontaneous non-aneurysmal SAH as the initial and only presenting neurologic event, raises the question of whether it can indeed be considered as a primary manifestation of COVID-19 in the absence of the more commonly reported respiratory and neurologic symptoms.

Fever is a known consequence of subarachnoid hemorrhage due to underlying systemic pro-inflammatory state and changes in thermoregulation brought about by the extravasated blood. The patient had no febrile episodes prior to consult and was only noted to have elevated temperature in the initial evaluation at the emergency department. It is unclear if the febrile episode is secondary to the then undetected SARS-CoV-2 infection or SAH. The elevated temperature is an independent factor for a poorer prognosis. The initial hypotensive episode, in the absence of clinical factors that may suggest sepsis, negates the argument that the spontaneous SAH could be a consequence of an uncontrolled hypertension which is consistent with the linear positive association of SAH to hypertension [14-16]. Normal coagulation studies support the absence of coagulopathy at the time of the study. A study by Can et al. [17] showed the association of aspirin and decreased risk of aneurysmal rupture possibly via stabilization of aneurysm wall and countering the pro-inflammatory state. High levels of cyclooxygenase-2 and microsomal prostaglandin E2 synthase-1 associate aspirin's known mode of action with its protective effect in stabilization of aneurysms. Aspirin is known to delay thrombus formation, aneurysmal wall inflammation and endothelial injury. After the rupture of an aneurysm, aspirin use may increase the risk of re-bleeding [17,18]. In light of this, had this case been an episode of SAH secondary to a ruptured aneurysm on a background of medication use that could, generally, increase the risk of bleeding, the patient's prior antiplatelet therapy may, if any, contribute little to the neurologic event. Single antiplatelet therapy use (in this case, aspirin, which increases risk of intracranial hemorrhage by 0.1% per year) is associated with low risk of major bleeding [19].

D-dimer elevation in patients with COVID-19 signifies hyper-fibrinolytic, pro-inflammatory state and is known to correlate with disease severity and may increase the risk of intracranial hemorrhage [20]. Increased D-dimer level promotes fibrinolytic function and plasmin generation in microvascular lesions of intracranial hemorrhage which may inhibit hemostatic function and cause hypercoagulable state. In our case, elevated D-dimer was noted at the onset which may be attributed to a then undetected COVID-19 infection. This might not be a direct, independent causation, however, its association with the resultant hemostatic dysfunction may provide insight on possible correlation of increased fibrinolytic activity with development of spontaneous SAH in patients with COVID-19.

Amyloid (Aβ) deposition, such as that seen in Cerebral Amyloid Angiopathy (CAA), could cause fragility of blood vessels, thereby increasing the risk of intracerebral hemorrhages. Presentation may vary, ranging from incidental micro bleeding to frank manifestation of neurologic symptoms including sensorium changes, headache, seizures and focal deficits. Coexistence of Alzheimer's disease neuropathologic change (ADNC) and CAA is present 78%-98% of individuals. Clinically, the most common manifestation is spontaneous lobar hemorrhage. Boston criteria combines clinical, radiologic and pathologic findings to assess the probability of CAA; however, definitive diagnosis necessitates post-mortem brain examination [21-24]. The review of the clinical history of patient revealed no prior presentation of cognitive dysfunction or dementia, hence, CAA was not considered as one of the initial impressions. Moreover, CAA usually presents with lobar intracranial hemorrhage and not SAH.

The possibility of a hospital-acquired infection was practically ruled-out since patient underwent testing for COVID-19 on the day of the consult. RT-PCR result for SARS-CoV-2 shows detectable viral RNA 2 to 8 days after contracting the virus [25]. With this information, the patient's infection must have been present for at least 2 days prior to the initial consult and is consistent with the known incubation period of the virus of 2 to 7 days (can be up to 14 days) [26].

Conclusion

The authors viewed these events as an undetected COVID-19 in an otherwise initially asymptomatic patient who presented with a transient altered sensorium secondary to a non-traumatic, non-aneurysmal SAH, with subsequent manifestation to critical pneumonia leading to ARDS. Other factors that could otherwise explain the development of spontaneous SAH outside the context of COVID-19 was reviewed with limited literatures, albeit a hypocaoguable state due to elevated D-dimer is suspected. Further epidemiological and clinical studies are warranted to clearly establish spontaneous SAH as an initial manifestation of COVID-19.

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