Severe Intractable Headache as a Presentation of COVID-19 in a 23-Year-Old

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Severe acute respiratory syndrome coronavirus type 2 is a novel betacoronavirus with a new genome sequence that causes coronavirus disease 2019 (COVID-19), which primarily affects the lungs, thus causing pneumonia which can progress to severe acute respiratory distress syndrome. New emerging cases of extrapulmonary manifestations of COVID-19 include gastrointestinal, cardiac, renal, and/or central nervous system involvement. Although an ischemic stroke converting to a hemorrhagic stroke is more commonly seen, spontaneous intracranial hemorrhage (ICH) in hospitalized COVID-19 patients is on the rise. This case report describes a 23-year-old female who tested positive (via a polymerase chain reaction test) for COVID-19 and presented with new onset of severe intractable headache. The investigation suggested COVID-19 as the most probable cause of this patients' spontaneous ICH. This case emphasizes the importance of adding COVID-19 to the differential diagnosis of hemorrhagic cerebrovascular accidents in patients with a spontaneous ICH of unclear etiology and, in the process, performing COVID testing. [*P R Health Sci J 2022;41(2):100-103*]

Key words: COVID-19, hemorrhagic stroke, intracerebral hemorrhage (ICH), cerebrovascular accidents (CVAs)

Severe acute respiratory syndrome coronavirus type 2 is a novel betacoronavirus with a new genome sequence that causes coronavirus disease 2019 (COVID-19) (1). The viral outbreak started in Wuhan, China, in December 2019. The virus affects primarily the lungs, thus causing pneumonia, which can progress to acute respiratory distress syndrome and may lead to death secondary to respiratory failure. New emerging cases of extrapulmonary manifestations of COVID-19 include gastrointestinal, cardiac, renal, and/or central nervous system (CNS) involvement. Recent complications in COVID-19 that affect the CNS include encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic stroke, cerebral venous sinus thrombosis, and intracerebral hemorrhage (ICH) (2). Although an ischemic stroke converting to a hemorrhagic stroke is more commonly seen (6), spontaneous ICH in hospitalized COVID-19 patients is on the rise. Therefore, learning about the clinical characteristics, pathogenesis and risk factors of COVID-19 induced-ICH is imperative, especially as it has such high morbidity and mortality.

Case Report

This is the case of a 23-year-old female G0P0A0 undergraduate student with no past medical, surgical history or toxic habits who complained of a constant, severe, pulsatile right orbital headache that radiated to the back of the head since three days of evolution. The headache worsened with scalp palpation and was refractory to over-the-counter (OTC) medications. Associated symptoms were nausea, dizziness, and problems concentrating. She denied the presence of fever, chills, blurry vision, vomiting, auras, photophobia, phonophobia, head trauma, rashes, oral ulcers, weight loss, previous deep vein thrombosis, or pulmonary embolism. Her family history was noncontributory, as there was no history of thrombophilia or systemic lupus erythematosus (SLE). Due to persistence of headaches, she sought help at a peripheral hospital, where a COVID-19 PCR assay from a nasopharyngeal swab was incidentally found to be positive. She was transferred to our institution to receive a neurosurgical evaluation after a head computed tomography (CT) scan showed an ICH. She was sexually active with one male partner but denied the use of oral contraceptive pills. Four weeks prior to our evaluation, she traveled to Orlando, Florida, USA and spent time with her family members. During her stay in Florida, she experienced a runny nose, anosmia, pleuritic chest pain, subjective fever and chills. Her flu-like symptoms improved with OTC medications, reason for which she never sought medical

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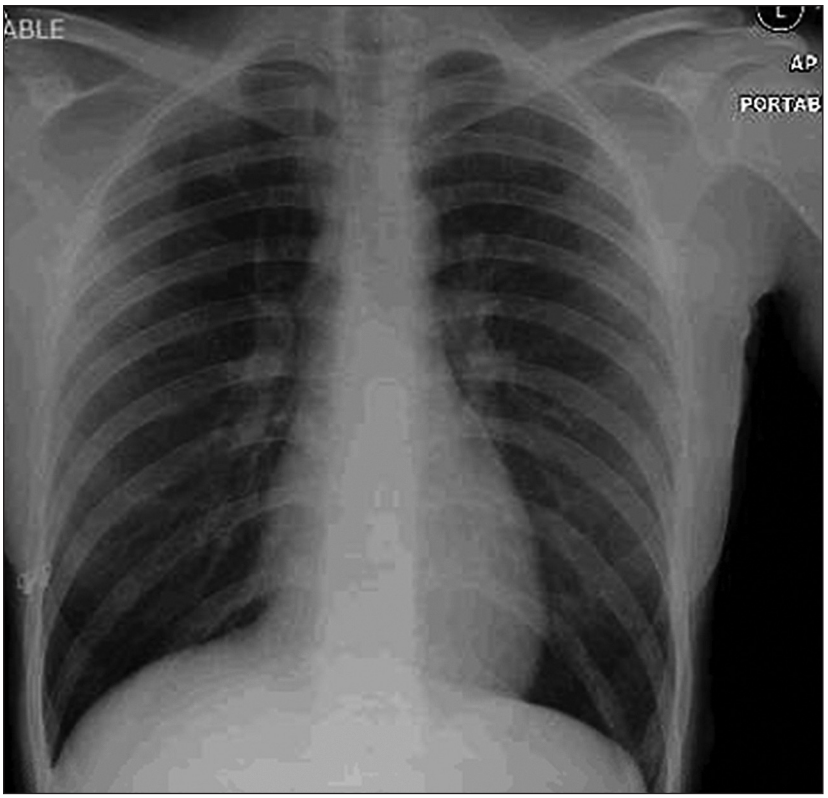

Figure 1. Portable erect anteroposterior chest x-ray of the patient.

attention. Upon evaluation, the patient was afebrile, non-tachycardic, normotensive, and breathing at room air. Her peripheral oxygen saturation was 100%. She seemed in moderate distress due to her headaches but without focal or gross neurological deficit. A complete blood count (CBC) was remarkable for normocytic normochromic anemia (11.2 g/dL) with normal blood morphology, and mild thrombocytopenia of 159 Thou/uL (normal range 163-369 Thou/uL). No electrolyte disturbances or acid-base disorders were identified. Her hepatic enzymes were mildly elevated (aspartate aminotransferase: 159 U/L; alanine aminotransferase: 116 U/L). Coagulation studies were within normal limits. Arterial blood gases and inflammatory markers, including sedimentation rate, c-reactive protein, d-dimer, and ferritin, were unremarkable. A COVID-19 PCR test and a mycoplasma immunoglobulin M (IgM) test were both positive. A chest x-ray (CXR) was unremarkable, with clear costophrenic angles and no consolidations, effusions, or ground-glass opacities (Figure 1). The head CT showed an intraparenchymal hemorrhage in the precuneus area of the right parietal lobe without evidence of a prior ischemic event (Figure 2). A head CT venogram (CTV) and arteriogram (CTA) were both negative for thrombosis and vascular malformation, respectively. In view of this unusual clinical presentation, immunologic (antinuclear antibodies, anti-cardiolipin, and beta 2 glycoprotein IgG/IgM/IgA), hematologic (Von-Willebrand, antithrombin III, factor V Leiden and proteins C and S), and infectious (mycoplasma cold agglutinins, HIV, and hepatitis) workups were performed and found to be negative. Therefore, these other etiologies were excluded before attributing the ICH to COVID-19. The patient was placed in isolation for seven days. During that time, she completed treatment for mycoplasma with oral Doxycycline and received analgesics for her headaches. A head CT was repeated at the fifth day of hospitalization due to ongoing refractory headaches. The CT imaging was unchanged, with no evidence of ischemia or rebleeding. The patient was discharged home with supportive care.

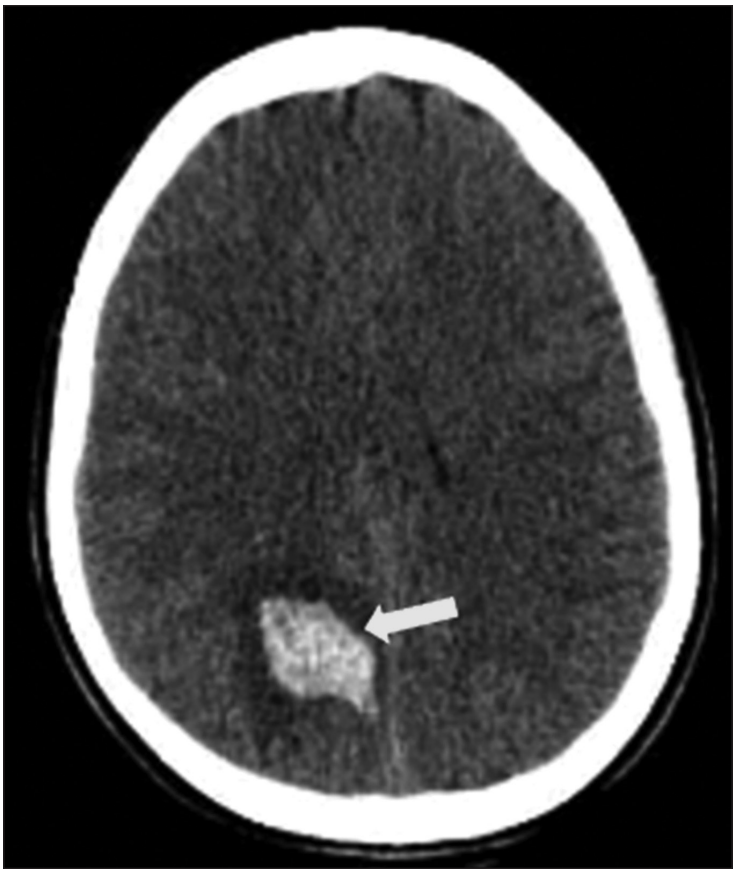

Figure 2. Head computed tomography scan (without contrast) of the patient. A hyperdense lesion in the precuneus area of the right parietal lobe (white arrow).

Discussion

Isolated cases of spontaneous ICH in COVID-19 patients have been reported in the literature. Most of these cases were males (65.8%) who were from 31 to 78 years of age, and 71% had been admitted due to respiratory symptoms of COVID-19, with an interval of 2 to 25 days between the onset of symptoms and the diagnosis of ICH (3). Furthermore, the majority had multiple comorbidities, including hypertension and diabetes mellitus (4). In Pavlov et al (2020), only 3 of 1,200 hospitalized COVID-19 patients had radiological evidence of ICH; patient #1 was a 50-year-old male, patient #2 was a 64-year-old male and patient #3 was a 60-year-old male. All of them had a prior diagnosis of hypertension, along with severe COVID-19 pneumonia symptoms (oxygen requirement and bilateral ground-glass opacities on chest CT). In addition, they all had increased inflammatory markers and thus a higher propensity for hemorrhagic complications (2). In the patients who participated in Pavlov's study and were admitted because of their neurological symptoms, the most common chief complaints were loss of consciousness and severe headaches (3). According to the American Heart Association COVID-19 Cardiovascular Disease registry, patients with COVID-19 diagnosed with ICH were mostly male (73%) and, compared to patients without ICH, were nominally older (≥ 65 years old) and had more vascular risks factors (4).

Contrarily, our patient had a completely different demographic characteristics from those of the patients described in the available literature, as she was a young female with no risk factors for ICH and no inflammatory markers or coagulation abnormalities.

The strongest proposed mechanism by which COVID-19 translocate to the CNS is by direct invasion of the olfactory bulb through the nasal cribriform plate (5). The inflammatory process elicited by the virus causes damage to the blood-brain barrier, which increases virus permeability and, therefore, neuroinvasion (4). This mechanism could explain the anosmia, which is a common symptom in COVID-19 patients. Once the virus reaches the CNS, it enters the vascular endothelial cells, neurons, and glial cells using its spike protein to bind angiotensin converting enzyme (ACE) 2 receptors (6). Their damage causes impairment in the sympathoadrenal system (downregulation of the ACE-2 and, in turn, overactivation of the renin-angiotensin system), causing damage to blood pressure regulation. This inflammatory response can lead to damage and weakening of the vascular walls, increasing the likelihood of rupture and, thus, an ICH (7,8,9). Another suggested mechanism is the activation of the inflammatory and hypercoagulable mechanism, which may contribute to a thrombotic state and vasculitis, both leading to ICH (7).

At this point, it is essentially impossible to categorically diagnose ICH solely secondary to COVID-19, both because increasing data and trends of diagnosis are being discovered and because there are no true criteria for diagnosis. Therefore, the attribution of the spontaneous ICH secondary to COVID-19 seen in this 23-year-old was a diagnosis of exclusion. In our case, we arrived at this diagnosis only after having done an extensive workup that considered immunological, hematogenous and infectious causes – all of which were ruled out.

Our patient had a positive COVID-19 PCR test and a Mycoplasma Pneumonia (MP) IgM test with negative cold-agglutinins. The negative cold agglutinins made mycoplasma an unlikely contributor to ICH because it is the presence of the agglutination of antibodies in serum that produces clotting abnormalities and, thus, ischemia (10). Therefore, MP with positive cold agglutinins has been linked more to ischemic strokes than to spontaneous intracranial hemorrhages. Moreover, in the pediatric population, most cases of cerebrovascular accidents (CVA) secondary to MP are accompanied by a prothrombotic state and hemolytic anemia. Although the co-infection of COVID-19 and MP was present, a synergistic effect causing an ICH was unlikely due to the absence of a prothrombotic state, hemolytic anemia and negative cold agglutinins, as well as there being no evidence of thrombi in head CTA or CTV.

This case report creates awareness of the spectrum of manifestations of COVID-19, which now includes spontaneous ICH as another possible consequence of this deadly virus. Being young with an absence of comorbidities does not exempt patients from having a CVA. This case strongly suggests the importance of considering COVID testing in patients with a spontaneous ICH of unclear etiology, thus adding COVID-19 to the differential diagnosis of causes of CVA. Additionally, unusual cases such as this one will help to expand the registry of the baseline characteristics of positive COVID-19 patients with ICH. At the same time, will create awareness in order to reduce the delay in diagnosis, thus preventing transmission to health personnel.

Resumen

El Coronavirus tipo 2 causante del Síndrome Respiratorio Agudo Severo (SARS-CoV-2) es un betacoronavirus novel con un nuevo genoma que se manifiesta como la Enfermedad del Coronavirus 2019 (COVID-19) la cual primeramente afecta los pulmones causando así el Síndrome de dificultad respiratoria aguda (ARDS en sus siglas en inglés). Nuevos casos sobre manifestaciones extrapulmonares incluyen envolvimiento gastrointestinal, cardíaco, renal y del sistema nervioso central. Aunque los accidentes cerebrovasculares isquémicos que convierten a hemorrágicos son más comunes (6,8,9), los casos con sangrados intracerebrales espontáneos en pacientes hospitalizados con COVID-19 están en aumento. Presentamos el caso de una fémina de 23 años sin historial médico pasado con una prueba de Reacción en Cadena de Polimerasa (PCR en sus siglas en inglés) COVID-19 positiva con dolor de cabeza severo. Luego de descartar otras etiologías, nuestra investigación sugiere que el COVID-19 es la causa más probable de hemorragia cerebral espontánea, aunque la confirmación del diagnóstico es casi imposible. Este caso enfatiza la importancia de añadir

COVID-19 en el diagnóstico diferencial de pacientes jóvenes y sin factores de riesgo con hemorragias cerebrales espontáneas sin una etiología clara con la finalidad de siempre añadir las pruebas diagnósticas para COVID-19.

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