CASE REPORT: CEREBRAL VENOUS SINUS THROMBOSIS AND COVID-19 INFECTION

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Coronavirus disease-2019 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus). Coronavirus disease-2019 (COVID-19) was declared a pandemic in March 2020 and has changed our lives in many ways. This infection induces a hypercoagulable state leading to arterial and venous thrombosis, but the exact pathophysiology of thrombosis is unknown. However, various theories have been postulated including excessive cytokine release, endothelial activation, and disseminated intravascular coagulation (DIC). We present a patient diagnosed with cerebral venous sinus thrombosis (CVST) with COVID-19 infection. A 66-year-old man presented to a hospital for evaluation of persistent headaches. He tested positive for COVID-19, and MRI of the brain and CT venogram revealed CVST. He was started on heparin drip in the hospital and transitioned to oral anticoagulants at the time of discharge. His headaches improved with treatment. Even though headache is the most frequent and initial symptom of cerebral venous thrombosis, it is rarely the only symptom. A high index of suspicion is therefore required to diagnose CVST especially if the patient presents with a simple complaint like a headache. Common complaints can delay the diagnosis leading to disease progression. Considering the high mortality rates in patients diagnosed with CVST, we suggest the importance of knowing the association between COVID-19 infection and CVST, especially in susceptible patients.

Keywords: case report, cerebral venous sinus thrombosis (CVST), COVID-19, headache, anticoagulant

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has affected nearly every individual across the world. Thus far, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus infection has infected approximately 180 million individuals and has resulted in 4 million deaths. The transmission of the virus is through direct contact and by airborne droplets (1). The virus attaches to a site on the ACE2 receptor and then replicates in the cytoplasm of the cell, producing progeny virions (2, 3). These virions are released from the cell into surrounding tissues of the respiratory tract (4). They are usually shed by coughing or sneezing and the incubation period of the infection is between 4.5 and 5.8 days (5). ACE2 receptors are present in many organs and tissues including the lungs, trachea, bronchi, stomach, small intestine, sweat glands, parathyroid, pituitary, pancreas, and cerebellar endothelial cells (6, 7).

Clinical manifestations of COVID-19 range from an asymptomatic state to multiorgan dysfunction (8). COVID-19 affects the respiratory system causing progressive respiratory failure and organ dysfunction, leading to generalized coagulopathy (9–11). Most commonly, infection manifests with symptoms including cough, fever, diarrhea, fatigue, headaches, and myalgias.
Shortness of breath due to pneumonia is the most common symptom of hospital admission (12, 13). Respiratory failure, acute respiratory distress syndrome (ARDS), cardiac arrhythmias, coagulopathy, and shock are delayed manifestations of severe disease (14). Severe disease and progression are secondary to the release of inflammatory cytokines including interleukins (IL-2, IL-6, IL 7, IL 10), Granulocyte Colony Stimulating Factor (G-CSF), Interferon gamma-induced protein 10 (IP-10), MCD 1, M1 P18, and TNF alpha (15, 16).

Autopsies of infected patients have shown that the virus can cause microvascular injury in the brain (17). The mechanism by which the virus spreads to the brain is via the cribiform plate into areas surrounding the olfactory bulb, olfactory nerve, and through the blood-brain barrier (18–20). Neurological manifestations of Covid-19 range from headache to encephalopathy. The symptoms include headaches, dizziness, ageusia, weakness, and confusion. Patients with central nervous system involvement can be diagnosed with acute encephalopathy, acute cerebrovascular problems, acute ischemic stroke, hypoxia, Guillain-Barré syndrome (GBS), ataxia, olfactory disorders, gustatory dysfunction, seizures, psychosis, and cerebral venous sinus thrombosis (CVST) (21, 22).

Cerebral Venous Sinus Thrombosis

Cerebral venous sinuses are an uncommon location of venous thrombosis and are mostly observed in women and the younger population (23–25). Common causes of CVST include hereditary prothrombotic conditions, antiphospholipid antibody syndrome (APLS), cancer, pregnancy, autoimmune diseases, and infections (26). It can lead to increased intracranial pressure, encephalopathy, strokes, cranial nerve palsies, seizures, and headaches (27). The most common presentation of CVST is a headache and it can be the only symptom in some instances (26, 28–31). The etiology of headache is likely secondary to the compression of nerves within veins (32), increased intracranial pressure, or, sometimes, venous infarct (33, 34). It is often difficult to differentiate CVST-induced headaches from other primary headache disorders. Most headaches caused by CVST are subacute in onset, causing diffuse throbbing pain. Other associated neurological findings include neurologic deficits, photophobia, or signs of increased intracranial pressure (35–38). Sometimes CVST can also lead to damage of brain parenchyma (39).

Diagnosing CVST can be very difficult due to differences in clinical presentation and imaging findings. Only about 25% of patients with CVST can be diagnosed by unenhanced head CT. CT venography and MRI can be used if there is a high suspicion after unenhanced head CT. The European Academy of Neurology recommends intravenous heparin or subcutaneous low molecular weight heparin first followed by oral anticoagulation for at least 3 to 12 months depending on the etiology of CVST (31).

CVST AND COVID-19

Coronavirus disease-2019 infection causes a hypercoagulable state, resulting in increased inflammatory markers like D-dimer, Lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP). It also causes an increase in clotting times (40–44). Usually, prothrombotic events including deep vein thrombosis (DVT) and pulmonary embolism occur later as the disease progresses. Many studies have shown an association of COVID-19 infection with CVST (45–48). The most common location of CVST secondary to COVID-19 infection is the transverse sinus followed by the sigmoid sinus (49). The severe microvascular injury in COVID-19 infection is suggested to be due to the combined effect of complement activation and hypercoagulability, leading to microvascular thrombosis. The cerebrovascular effects also seem to be secondary to hypercoagulability and endothelial injury resulting from the release of pro-inflammatory cytokines. Some patients diagnosed with CVST in COVID-19 infection present elevated anticardiolipin IgM antibody and lupus anticoagulant. They also had increased fibrinogen levels, inflammatory markers, and prothrombin time (50–57).

CASE DISCUSSION

A 66-year-old man with a past medical history significant for GERD, hypothyroidism, previous head and neck cancer status, post-resection history chemotherapy, and radiation presented to the hospital for evaluation of headaches. The patient reported waking from sleep with a pounding headache two to three times per month over a 6-month period. The headaches were associated with palpitations, dizziness, and diaphoresis. He denied any complaints of blurred vision, slurred speech, weakness, numbness, or tingling of his extremities, nausea, and vomiting. He reported no complaints of shortness of breath, cough, nasal congestion, fatigue, or diarrhea. His pain was reportedly resolved by two to three tablets of ibuprofen 200 mg. While his headaches did not significantly impact his activities of daily living, they did prompt discussion with his primary care physician. An outpatient MRI brain was performed, which revealed findings suspicious of CVST. Thus, he was sent to the emergency department for further evaluation.

Three months prior to admission, the patient was tested for SARS-CoV-2 virus infection from a potential exposure at work. He tested positive and exhibited symptoms of cough, headache, and nasal congestion. He never exhibited significant shortness of breath or pleuritic chest pain. His symptoms improved with basic medical management. On his current admission, he was again tested for COVID-19 and tested positive. He denied a history of smoking, alcohol abuse, or recreational drug use. He had a past medical history of cancer on the base of the left tongue.
involving the left tonsils and left neck lymph nodes which was treated by surgery, radiation, and chemotherapy 11 years prior. He never presented any signs or symptoms of recurrence. Family history was not significant. His body mass index at the time of admission was 28 kg/m², vital signs were within normal limits, and he was saturating well on room air. Physical examination including complete neurological examination was within normal limits. CBC revealed hemoglobin of 12.3, BMP revealed mild elevation of potassium was 5.2 mg/dl, TSH was within normal limits. His IgG, IgM, and IgA beta-2 glycoprotein antibodies were all within normal limits. IgG, IgA cardiolipin antibodies were within normal limits, but IgM was mildly positive at 21. Factor V Leiden and prothrombin gene mutations were negative. On telemetry, the patient had a pattern of bigeminy and trigeminy. He had no complaints of chest discomfort; there were no signs of ischemia, and a subsequent two-dimensional echo was within normal limits. CT brain imaging without contrast revealed no acute intracranial hemorrhage, midline shift, or mass effect but showed parenchymal volume loss, which was a probable sequelae of chronic small vessel ischemic change, as expected for age of the patient. There was no evidence of recurrence of his known cancer. MRI brain findings showed an abnormal FLAIR signal with loss of flow void in the distal left transverse sinus, sigmoid sinus, and jugular bulb (Figure 1). This was followed by a CT venogram, which revealed a filling defect in the left sigmoid sinus, jugular bulb, and visualized left internal jugular vein compatible with dural venous sinus thrombosis (Figure 2). He was started on intravenous heparin for dural sinus venous thrombosis. Prior to discharge, he has transitioned to Rivaroxaban 20 mg with anticipated treatment lasting 6 months. His symptoms had resolved at the follow-up appointment 3 months later.

**DISCUSSION**

Coronavirus disease-2019 usually manifests as fever, dyspnea, cough, diarrhea, and fatigue. The most common thromboembolic complications with COVID-19 infection are DVT and pulmonary emboli (47, 58). CVST is a rare thromboembolic event in the setting of COVID-19 disease, but the neurologic complications can sometimes be very severe if not diagnosed and treated early in the disease course (59, 60). The amount of CVST burden in hospitalized patients with SARS-CoV-2 infection was 0.08% with a 95% CI of 0.01 to −0.5
in a meta-analysis. It was also noted in the same study that risk factors other than SARS-CoV-2 infection were present in 31% of these individuals (59). Most patients presenting with CVST do not have a history of thrombotic disorders (58). Hereditary and acquired prothrombotic conditions like factor V Leiden, G20210A prothrombin gene mutation, malignancy, oral contraceptive use, pregnancy, and infection increase the risk of CVST compared to the general population (23). CVST complication in COVID-19 positive patients can present as loss of consciousness (37, 61), upward gaze (37, 61), visual deficits (60), convulsions (62), hemiparesis (62), headache (62, 63), executive dysfunction (63), dyspraxia (63), tongue biting (61), altered mentation (64), and aphasia (64). However, headache is the most common presenting symptom in patients with CVST (48). With advances in neuroimaging modalities, diagnosing CVST has become straightforward, however, early recognition of CVST is often obscured due to a wide variety of symptoms. Our case report presents headache as a manifestation of CVST associated with COVID-19. CVST can have symptoms from very mild to very severe. Headache is a common symptom in most viral illnesses and headache syndromes, therefore, a thorough evaluation is needed to rule out common problems before proceeding with expensive imaging studies. But new-onset recurring headaches need a high index of suspicion for treatable conditions like CVST as we can improve outcomes in such patients. Our patient had a previous history of cancer, and about 7–10% of patients diagnosed with CVST have cancer (65). Even though it is unlikely that his treated cancer which is in remission caused CVST, it is important to note that cancer increases the risk

FIGURE 2 | CT Venogram: filling defect in the left distal transverse sinus, sigmoid sinus, and jugular bulb, compatible with occlusive dural venous sinus thrombosis.
of thrombosis (66). The mortality rate of CVST associated with COVID-19 virus infection is significantly high (67, 68). Thus, in this pandemic era, even a symptom as common as a new-onset persistent headache should be investigated further as it may sometimes represent a medical emergency. In conclusion, timely recognition and awareness of this association enable prompt diagnosis and treatment with good clinical outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

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ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MA wrote the case report under the guidance of MM. MM is the Hematologist who treated the patient. SW is the Neurologist involved in the care of the patient. LJ and AS from radiology were responsible for the interpretation of images. All authors were involved in making appropriate changes as needed and approved the final case report.
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