Reversible Cerebral Vasoconstriction Syndrome in the Setting of COVID-19 and Pleomorphic Sarcoma
A Case Report

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INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is an increasingly recognized clinical and radiologic syndrome. However, it has been rarely reported in the setting of the novel coronavirus disease-2019 (COVID-19) infection in sarcomatous tumors. RCVS might be the initial manifestations of COVID-19 infection or noncatecholamine-producing masses including sarcoma.

CASE REPORT

A 44-year-old male who developed COVID-19-related symptoms followed by rapid onset of severe headaches in the setting of persistently elevated blood pressure (BP). Brain imaging showed multifocal arterial narrowing in the anterior and posterior circulation consistent with RCVS. Serial imaging demonstrated resolution of the arterial narrowing after BP control was achieved with improvement in the patient’s headaches.

Further investigation for secondary causes of the patient’s elevated BP revealed a right renal mass, and the patient underwent right nephrectomy, and the biopsy results confirmed the diagnosis of pleomorphic sarcoma.

CONCLUSION

Our case suggests a possible association between severe acute respiratory syndrome coronavirus 2 with development of RCVS, but further studies are needed to validate this observation, establish a causal relationship, and define a pathophysiological mechanism. Considering tumors other than catecholamine-producing masses as a potential risk factor for developing RCVS might lead to earlier detection and treatment of any underlying malignancy in patients whom the main and sole presentation could be RCVS.

KEY WORDS: reversible cerebral vasoconstriction syndrome, COVID-19, pleomorphic sarcoma, headache

BACKGROUND

Reversible cerebral vasoconstriction syndrome (RCVS), or Call-Fleming syndrome, is an increasingly recognized clinical and radiographic syndrome characterized by severe thunderclap headaches with or without focal neurological symptoms, occurs in the setting of cerebral vasoconstriction that typically resolves within a period of 3 months. Clinical presentations range from benign isolated cephalalgia to rare lethal forms, but headache is the main symptom and often remains the only manifestation. RCVS can occur spontaneously, but in up to 60% of cases a specific trigger can be identified, most importantly vasoactive medications, illicit drugs or postpartum state. While the exact etiology is unknown, transitory dysregulation of the cerebral vascular tone because of various hormonal and biochemical factors have been described as the most likely pathomechanism. The condition is usually self-limited, and recurrence is rare. However, progressive and fulminating cases have been reported in minority of patients.

Coronavirus disease-2019 (COVID-19) infection has been associated with various neurological manifestations, including altered mental status, acute cerebrovascular diseases, and postinfectious Guillain-Barre syndrome. An association with RCVS has not been widely reported in the literature with only one case report of concurrent RCVS in the setting of the novel COVID-19 infection being published at the time of this writing. Occurrence of RCVS in the setting of malignancies has been reported, with the most common entities including pheochromocytoma and secretory parangangioma. However, no clear association with sarcoma has been described thus far. Here, we present the intriguing case of a patient with RCVS occurring in the setting of COVID-19 infection and pleomorphic sarcoma.

CASE REPORT

A 44-year-old man was transferred to our tertiary care center for management of refractory headaches and elevated blood pressure (BP). He was independent at baseline and had no significant past medical history other than intermittent cannabis use and major depressive disorder treated with duloxetine. One month before the presentation, he was exposed to a family member with active COVID-19 infection. His symptoms started a few days later with loss of sense of smell and taste and developed mild upper respiratory tract symptoms. This was followed by rapid onset of severe bifrontal headaches that have since been present intermittently and have been progressive despite symptomatic treatment with simple analgesics.

In the emergency department, his BP was 195/126, nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on reverse transcription polymerase chain reaction assay, comprehensive metabolic panel showed elevated creatinine of 1.58 mg/dl, hyponatremia of 129 mmol/l. Urine drug screening was positive for tetrahydrocannabinols and noncontrast head computed tomography (CT) was negative for acute intracranial abnormalities. Shortly following admission, a stroke alert was activated for acute onset of language difficulty. On examination, his BP was 170/107 and the National Institutes of Health Stroke Scale (NIHSS) was 2 for moderate to severe expressive aphasia. A repeat noncontrast CT head
showed no evidence of intracerebral hemorrhage or early acute ischemic changes. CT angiogram of the head and neck was negative for large vessel occlusion, however, it did demonstrate focal narrowing in the left posterior cerebral artery near the P2-P3 junction, focal narrowing just beyond the origin of the superior division of the left middle cerebral artery and subtle narrowing of the proximal M1 segment of the right middle cerebral artery concerning for RCVS (Fig. 1). The stroke alert was subsequently downgraded as the patient appeared encephalopathic and his language dysfunction was attributed to hyponatremia and persistent elevation in BP. He was transferred to the intensive care unit for further management of hyponatremia and agitation.

During his intensive care unit stay, renal ultrasound was performed because of persistently elevated BP and showed a heterogenous mass infiltrating the right kidney with invasion into the adjacent liver. CT abdomen and pelvis with intravenous contrast displayed a hypoenhancing right renal mass of 18 cm diameter that was replacing the right kidney with intrahepatic invasion along the subcapsular surface of the liver (Fig. 2). A magnetic resonance angiogram of the brain, performed few days later, showed resolution of intracranial vessel narrowing (Fig. 1). The patient’s BP was well controlled on nicardipine drip then oral nifedipine, and his headaches gradually improved over the course of admission. The patient underwent right nephrectomy with tumor resection, and the biopsy showed findings consistent with pleomorphic sarcoma (Fig. 2). At the time of discharge, the patient was free of headaches.

DISCUSSION

Here we present a case of patient with RCVS in the setting of COVID-19 infection and pleomorphic sarcoma. Only limited data exists regarding the association of RCVS with COVID-19 infection or malignancy. Dakay et al described the first and only case report of RCVS complicated by convexal subarachnoid hemorrhage in the setting of COVID-19 infection in a female patient who presented with severe cough and thunderclap headaches, and suggested a possible association between RCVS and SARS-CoV-2 infection. In addition, multiple published cases related the presence of tumor or their treatment with RCVS and suggested that tumors should be considered as a potential risk factor for developing RCVS although some of these tumors are nonfunctional, but none has been published so far in the setting of sarcoma.

Our case is unique as it is only the second of its nature to report the association of RCVS in the setting of COVID-19, and the first to report its association with pleomorphic sarcoma. It also illustrates the etiological heterogeneity of RCVS as it is not a single a disease entity, but a common presentation of multiple disorders characterized by reversible vasoconstriction of the cerebral vasculature. Dysregulation of the cerebral vascular tone leading to vasoconstriction has been implicated to be the key pathophysiological mechanism underlying RCVS. Estrogen, placental growth factor, endothelin-1, serotonin, nitric oxide prostaglandins have been suggested to be associated with the dysregulation.

More recently, COVID-19 has been shown to use angiotensin converting enzyme II receptor for cell entry. In the brain angiotensin converting enzyme II receptors are expressed in the
neurons inside the blood brain barrier, but it is also expressed in the circumventricular organs and cerebrovascular endothelial cells, and the control of central and peripheral sympathetic activity is one among the various functions of Angiotensin II in the brain. Dysregulation of this system in the brain by SARS-CoV-2 has been implicated in the pathogenesis of COVID-19-related acute ischemic strokes through overactivity of angiotensin II and its vasoconstrictor effect on cerebral vessels. It is possible through dysregulation of the angiotensin system in the brain, COVID-19 can lead to transient alterations in the cerebral vascular tone and lead to vasoconstriction and ultimately RCVS. However, more observational and prospective studies are needed to validate this observation.

RCVS has been described in the past in the setting of metanephrine-producing masses, especially pheochromocytoma and paraganglioma proposing that earlier diagnosis of these catecholamines producing tumors has the potential for reducing neurological morbidity and mortality as RCVS is a serious but reversible and treatable cerebrovascular manifestations of these tumors. In addition, it has been reported in the setting of nonmetanephrine producing tumors or their treatment such as breast cancer, colon cancer, uterine fibroids, and medulloblastoma. By the time of reporting this case, there have been no cases of RCVS associated with sarcoma and our case is the first one to describe such association. Although there is no clear pathophysiological relationship between these nonfunctional tumors and RCVS, oncological diseases, the noncatecholamine producing ones should be considered as a potential risk factor to decrease the rate of undiagnosis and to lead to earlier treatment and better prognosis.

Limitations of our case report include the presence of other traditional risk factors of RCVS in our patient: the intermittent use of marijuana and the presence of serotoninergic medication duloxetine. However, the temporal relationship between COVID-19 infection and the detection of the renal mass, and the development of RCVS argues that SARS-CoV-2 and the pleomorphic sarcoma may have been associated with RCVS in this case. Another limitation is the mild angiographic abnormalities of vessel narrowing which might question the diagnosis of RCVS in this case, but our patient’s calculated RCVS score, an approach to distinguish RCVS from other intracranial arteriopathies developed by Rocha et al. is 8 points (5 for recurrent severe headache, and 3 for the presence of vasoconstrictor trigger), with a score of 5 or higher having a high specificity and sensitivity (99% and 90%, respectively) for diagnosing RCVS. In addition, the mild angiographic abnormalities in our reported case is consistent with prior observations that patient without any brain lesion related to RCVS, had the mildest angiographic abnormalities.

**CONCLUSION**

The reported case is the first in the literature to suggest an association between RCVS and sarcomatous tumors. It also suggests a potential association between the novel COVID-19 infection and development of RCVS.

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