Case Report

Pituitary Apoplexy Secondary to Thrombocytopenia due to Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Report of a Rare Case and Literature Review

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Abstract

Purpose: To report a 16-year-old female patient with pituitary apoplexy in the setting of coronavirus disease 2019 (COVID-19) infection-related thrombocytopenia in the absence of preexisting pituitary macroadenoma.

Methods: The patient had been admitted because of respiratory complications of COVID-19 infection and developed thrombocytopenia, intense headache, and symptoms of cavernous sinus syndrome.

Results: Urgent magnetic resonance imaging of the brain depicted a pituitary apoplexy.

Conclusion: This case indicated that thrombocytopenia due to COVID-19 could be a predisposing factor for pituitary apoplexy in the absence of underlying pituitary disease.

Keywords: Coronavirus disease 2019, Pituitary apoplexy, Severe acute respiratory syndrome coronavirus 2, Thrombocytopenia

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19)-related disease is a febrile respiratory disease with various extrapulmonary manifestations including different direct and indirect neurological problems. This infection, in some cases, could cause coagulation-related abnormalities, especially thrombotic events and inflammatory reactions, but spontaneous bleeding was reported infrequently in this situation. [1]

Pituitary apoplexy is a rare condition due to hemorrhage or infarction of the pituitary gland that usually occurs secondary to pituitary macroadenoma (2%–12%). Characteristic features include the abrupt onset of headaches, cranial nerve palsies, and hypopituitarism. These neurological presentations are often due to a rapid increase in pituitary gland volume within the restricted space of sella turcica. [2] Here, we present a case of pituitary apoplexy in the setting of COVID-19-associated thrombocytopenia without any pituitary gland-related risk factor.

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Case Report

A 16-year-old female who had been admitted because of respiratory complications of COVID-19 infection was introduced to the neuro-ophthalmology clinic complaining of sharp, retro-orbital headache, diplopia, left eyelid swelling, and mild ptosis having started a day earlier. The patient had a

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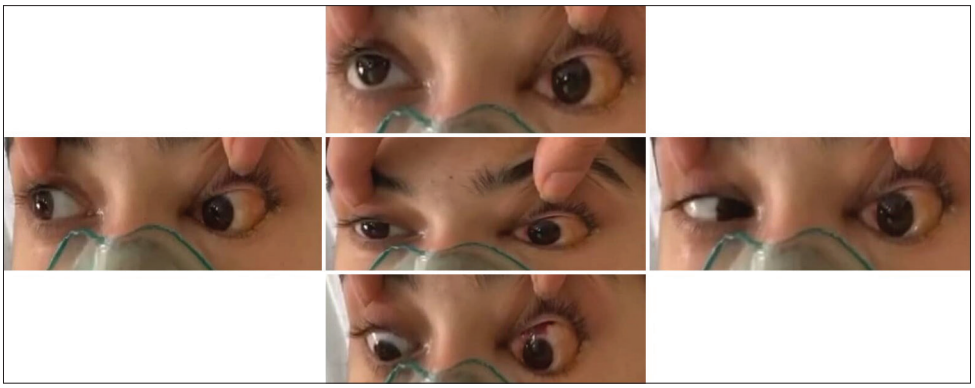

Figure 1: Partial left ophthalmoplegia and ptosis

history of upper respiratory tract infection symptoms 10 days before consulting and was confirmed positive for COVID-19 by a nasopharyngeal polymerase chain reaction swab test. Her past medical history was unremarkable. The vital signs were within normal limits. The ophthalmic examination revealed proptosis and chemosis at first glance. Visual acuity was 20/20 in both eyes, and color vision was also normal. Pupillary examination depicted anisocoria with the left pupil 5.5 mm in diameter and minimal reaction. The right pupil was 3.5 mm in diameter and reactive to light. No relative afferent pupillary defect was detected. Ocular motility examination was normal on the right side. Partial ophthalmoplegia due to the limitation of adduction, supraduction, infraduction, and abduction of the left eye suggested the involvement of the third and sixth cranial nerves on the left side [Figure 1]. The corneal and facial sensations were normal on both sides. Slit-lamp examination disclosed no abnormal finding in the right eye, but a superior subconjunctival hemorrhage and upper lid swelling and ptosis in the left eye were evident. The results of Goldmann applanation tonometry and funduscopic examination were normal in both eyes. Urgent magnetic resonance (MR) imaging of the brain was obtained, which revealed blood collection within the sellar region without compression of the optic chiasm. MR venography of the brain revealed no abnormality [Figure 2]. MR angiography of the brain was also unremarkable. Laboratory evaluation demonstrated thrombocytopenia (platelet count: 40000/μL) and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), which has been previously reported in COVID-19 infection.[3] During admission, the platelet count decreased dramatically to 25000 and then after about 1 week to 10000/μL, so additional tests were requested. Antithrombotic therapy was administered initially at the time of admission and then discontinued after the development of thrombocytopenia. Two peripheral blood smears were evaluated for the presence of schistocytes and other abnormal cells, but no morphologic abnormalities were found. Furthermore, the ADAMTS13 test results for the diagnosis of congenital or acquired thrombotic thrombocytopenic purpura were negative.

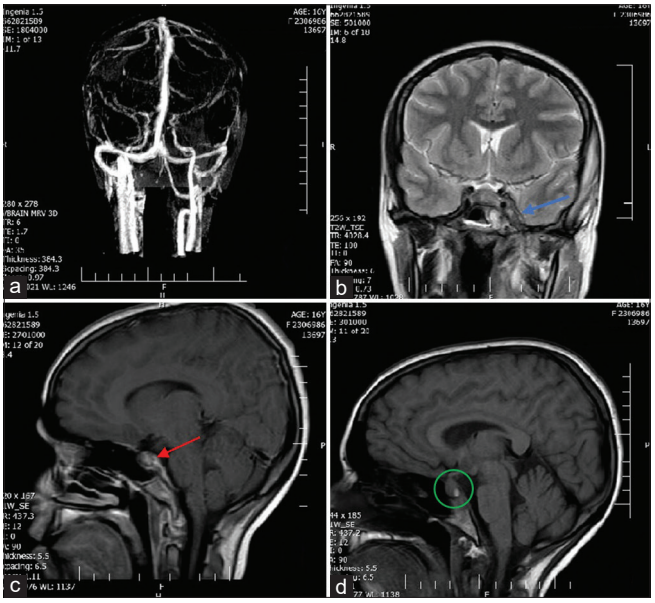

Figure 2: Unremarkable magnetic resonance (MR) venogram of the brain, with no evidence of venous sinus thrombosis (a). Coronal T2-weighted brain MR image depicts an asymmetrically expanded left cavernous sinus (blue arrow) (b). Precontrast sagittal T1-weighted brain MR image shows signal hyperintensity due to blood collection within the pituitary gland (red arrow) (c). Precontrast sagittal T1-weighted brain MR image demonstrates an approximately 15 mm × 20 mm sellar lesion without compression of the optic chiasm (green circle) (d)

After consulting with neurologists, the patient was transferred to the intensive care unit. Three days later, she experienced chest pain and shortness of breath. The body temperature increased to 38.5°C, and the respiratory rate was 30/min. Gradually, her level of consciousness decreased. A spiral computed tomography scan of the chest demonstrated massive pulmonary thromboembolism. Unfortunately, she passed away after 2 days.

Written informed consent was obtained from the patient's parents for participation in the study and publication of this report and related photos.

Table 1: Previously reported cases of pituitary apoplexy in association with Coronavirus disease 2019 infection

Author (s)/year	Gender	Age (years)	Signs and symptoms (including ophthalmologic findings)	Predisposing factor	Treatment	Final outcome
LaRoy and McGuire, 2021[1]	Male	35	Headache and neck stiffness, normal visual examination	Undetermined	Medical treatment	The patient was discharged
Chan *et al*., 2020[2]	Female	28	Blurry vision, dilated pupil, and headache	Pregnancy, previously undetected pituitary tumor	Transsphenoidal resection of the mass 2 days after vaginal delivery at 39 weeks was performed	The patient made a full recovery and was discharged
Bordes *et al*., 2021[12]	Female	65	Progressively worsening headache and persistent emesis, photophobia, and phonophobia	Undetermined	Medical treatment	The patient was discharged
Ghosh *et al*., 2021[15]	Female	44	Sudden-onset severe headache along with projectile vomiting and progressive asymmetric visual blurriness, subtly asymmetric bitemporal hemianopic visual field defects	Moderate thrombocytopenia and pituitary macroadenoma	Medical treatment (she refused surgical treatment)	The patient was discharged and was followed up
Solorio-Pineda *et al*., 2020[16]	Male	27	Progressive decrease in visual acuity, left exotropia, and intense headache	Pituitary macroadenoma	Medical treatment	The patient died shortly afterward, secondary to pulmonary complications
Martinez-Perez *et al*., 2021[17]	Female	54	Acute worsening headache with a new focal retro-orbital component, blurry vision	Previously undetected adenoma	Surgical adenoma resection, postoperative medical treatment	Visual acuity significantly improved
Martinez-Perez *et al*., 2021[17]	Male	56	Headache, altered mental status, complete third and fourth cranial nerve palsies	Obesity, lactotroph-type pituitary adenoma	Endonasal transsphenoidal microscopic resection of the sellar mass	The patient was discharged
Martinez-Perez *et al*., 2021[17]	Male	52	Acute headache, progressive peripheral vision loss	Lactotroph pituitary adenoma	Elective endoscopic transsphenoidal resection	The patient was discharged
Yazbeck *et al*., 2021[18]	Male	45	Severe thunderclap headache, blurred vision, palsies of the 3rd, 4th, and 6th cranial nerves	Invasive macroadenoma	Transsphenoidal resection of the sellar tumor	Medical treatment for panhypopituitarism
Yazbeck *et al*., 2021[18]	Male	28	Severe acute headache associated with a new-onset esotropia of the left eye	Adenoma	Transsphenoidal resection of the sellar tumor	The patient was discharged
Lesniak *et al*., 2021[19]	Female	38	Severe headache, nausea, vomiting, blurry vision, and ophthalmoplegia (3rd and 6th cranial nerve palsies, and bitemporal hemianopia)	Pituitary macroadenoma	Endoscopic transnasal transsphenoidal surgery	Complicated by a CSF leak, which required surgical repair and graft, and transient central diabetes insipidus treated with desmopressin
Liew *et al*., 2021[20]	Male	75	Severe frontal headache and a 1 week history of fever, periorbital tenderness	Pituitary adenoma	Medical treatment	The patient was discharged
Kamel *et al*., 2021[21]	Male	55	Progressive decrease in visual acuity and oculomotor nerve palsy	Pituitary macroadenoma resection 11 years ago (enlarging residual pituitary adenoma)	Endoscopic endonasal transsphenoidal resection	The patient passed away due to complications of severe COVID-19 pneumonia

COVID-19: Coronavirus disease 2019, CSF: Cerebrospinal fluid

Discussion

Pituitary apoplexy usually happens in the 5th–6th decades of life. Some of its known predisposing factors include trauma or head injury, coagulopathy, hypertension, pregnancy, or postpartum situation, major surgical interventions, anticoagulant therapy, and increased intracranial pressure.[4]

The increased tendency to bleeding in COVID-19 patients could be explained by systemic or local mechanisms.

Systemically, thrombocytopenia could be a result of the COVID-19 infection itself.[5,6] The incidence of thrombocytopenia on admission in COVID-19 patients (platelet count $<150 \times 10^9$/L) is 36.2%.[7] It has been generally believed

that thrombocytopenia is suggestive of disease severity, so a progressive decline in platelet count is meaningfully associated with increased mortality.[8] Some proposed mechanisms for thrombocytopenia are (1) direct infection of bone marrow cells by the virus and destruction and inhibition of platelet synthesis (because of a potential defect in hematopoietic microenvironment caused by systemic inflammation or cytokine storm, e.g., elevated interleukin-6 in SARS-CoV-2 infection)[9,10], (2) platelet destruction by the immune system activity (cross-reaction of antiviral antibodies with platelet integrin GP IIb/IIIa)[11], and (3) platelet aggregation in the lungs as microthrombi and thrombi causing platelet consumption.

Moreover, thrombocytopenia has been reported in the setting of several other infectious or hematologic diseases (such as Dengue hemorrhagic fever, idiopathic thrombocytopenic purpura, drug-induced thrombocytopenia, and hemolysis-elevated liver enzymes-low platelet [HELLP] syndrome), as the main cause of pituitary apoplexy.[5,6]

Platelet dysfunction and prolongation of prothrombin time/activated partial thromboplastin time can cause coagulopathies in the setting of COVID-19 infection and lead to bleeding tendencies. In general, COVID-19-associated coagulopathy appears as a hypercoagulable state more than a bleeding state; nevertheless, spontaneous hemorrhage could be in association with thrombosis in these patients.[12] In our patient, pituitary apoplexy occurred in combination with the thrombotic event of pulmonary thromboembolism with an interval of several days. This patient developed progressive thrombocytopenia, but thrombotic thrombocytopenic purpura, which may occur in the setting of COVID-19 infection, was ruled out.

Cerebrovascular hemorrhagic events are the most common type of hemorrhagic complication of COVID-19. Documented the presence of the virus in the cerebrospinal fluid could be a local possible mechanism of the bleeding tendency in the central nervous system (CNS). Several hypothetical routes facilitate the viral entry: nasal epithelium and olfactory pathway, direct entry from the cerebral circulation after crossing the blood–brain barrier, and angiotensin-converting enzyme inhibitor receptors on CNS cells, which simplify the adhesion of virus to cells.[12,13] Proposed mechanisms of hemorrhage in the pituitary region after the entrance of COVID-19 to CNS are (1) the fragility of the vasculature in the pituitary region that predisposes this location to hemorrhagic infarcts[2] and (2) infectious stress state itself, which could promote the stimulation of the pituitary gland, and in turn, may increase pituitary blood demand leading to apoplexy.[6]

Another important issue about this case was the third and sixth cranial nerve palsies that may occur due to the compression of the cavernous sinus resulting from the mass effect of apoplexy. Cranial nerve compressions within or outside the cavernous sinuses are two possible reported mechanisms for this complication. Direct compression of the cranial nerve III (because of its same horizontal plane as the pituitary gland) or cranial nerve VI involvement (at the level of Dorello's Canal) outside the cavernous sinus is possible.[14] Orbital apex syndrome should also be kept in mind in cases of multiple cranial nerve palsies and proptosis or chemosis, but brain imaging did not demonstrate the involvement of orbital apex in this case.

Table 1 shows, as far as we know, all previously reported cases of pituitary apoplexy in the setting of COVID-19 infection. Of the 13 patients with this complication, 5 were female. The most common predisposing factor was underlying pituitary macroadenoma. Four cases were under the age of 40 years. Headache and vision problems were the most common symptoms. All except two patients, who died due to pulmonary complications of COVID-19, recovered and were discharged. Contrary to our case, the only previously reported case of pituitary apoplexy in the setting of COVID-19-related thrombocytopenia had pituitary macroadenoma.[15-21] Our case developed pituitary apoplexy without any pituitary gland-related risk factor.

In conclusion, the COVID-19 pandemic is a rapidly developing infectious situation throughout the world that is associated with several endocrine and neurological disorders. This case could be considered a very rare manifestation of COVID-19 and could be added to the list of previously reported cases of SARS-CoV-2 infection and pituitary apoplexy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given her consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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