Coronavirus Disease 2019 (Covid-19) Outbreak and Pituitary Apoplexy

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Abstract

Background.

Pituitary apoplexy (PA) is a rare and potentially life-threatening condition characterized by pituitary hemorrhage, often in the setting of a preexisting pituitary adenoma. Risk factors and mechanisms associated to PA are poorly understood. Although involvement of the nervous system in SARS-CoV-2 infection causing intracranial hemorrhagic complications has been documented, the association between COVID-19 infection and PA has yet to be determined.

Methods

. From a prospectively collected database of patients with pituitary adenomas, we retrospectively reviewed the electronical medical records and scans of patients with pituitary apoplexy during the COVID-19 outbreak, since March 2020 to December 2020, that were treated at a tertiary care center.

Results.

Herein, we report three consecutive cases of patients with PA and concomitant COVID-19 infection. Most common symptom at presentation was headache and visual worsening. Included patients were successfully treated with surgical decompression and medical management of the hormonal deficits, experiencing moderate to significant improvement of their visual symptoms at last follow up. COVID-19 infection in the perioperative period was corroborated throughout polymerase chain reaction testing in all patients.

Conclusions.

COVID-19 positive patients may be at an increased risk of developing PA. Angiotensin-converting enzyme 2 receptors expressed in cerebrovascular endothelium may potentially play a role in the molecular mechanisms that induce changes of the vascular autoregulation and cerebral blood flow and predispose to pituitary hemorrhage in patients harboring a pituitary adenoma.

Introduction

Involvement of the nervous system in SARS-CoV-2 infection has been documented[1–3]. Latest evidence has suggested that patients with Coronavirus Disease of 2019 (COVID-19) are predisposed to developing ischemic stroke or intracranial hemorrhagic complications[4–6]. However, the strength of this association is weak, or can be partially explained by the presence of other confounding factors, such as the use of anticoagulation or the higher prevalence in critically ill patients[3, 4, 6–9].

Pituitary apoplexy (PA) is a rare and potentially life-threatening condition characterized by pituitary hemorrhage, often in the setting of a preexisting pituitary adenoma[10]. Clinically, this condition is characterized by the sudden onset of headaches, visual changes, and endocrine disturbances. While its incidence is relatively low in patients with pituitary adenomas, the pathophysiological mechanism of PA is poorly understood[11].

In this work, we report three consecutive cases of patients with pituitary apoplexy seen at a single tertiary care center who were all diagnosed with COVID-19 infection, during or shortly before admission, and discuss the relationship between these two conditions.

Methods

Between March 2020 and December 2020, three consecutive cases of patients with PA were admitted by a tertiary referral hospital for neurosurgical evaluation. Medical chart and imaging examinations were retrospectively reviewed. Special attention was directed towards the timeline between COVID-19 infection and the onset of symptoms that prompted evaluation for PA. These patients did not have concurrent intracerebral lesions (other than PA), did not suffer from additional neurological complications derived from COVID-19 infection, and did not receive anticoagulants prior to the diagnosis of PA.

These data were presented to the institutional review board of our institution, which waived the need for informed consent in light of the anonymized retrospective 3-case series design.

Results

Patient #1. A 54-year-old female, presented as a transfer from an outside hospital, complaining of one week of holocranial headache, acutely exacerbated (increasing intensity, new retro-orbital component to pain) two days prior to presentation. She denied diplopia, but she noted onset of blurriness in her right eye vision approximately 24 hours prior to presentation to the hospital. On neurologic examination patient was awake and alert. Cranial nerve examination was unremarkable. Her visual acuity was subjectively normal on the left, but she could only perceive light on the right. She underwent a head MRI scan demonstrating a hemorrhagic mass in the region of the sella turcica, with an enlarged sella and suprasellar extension, suggesting a previously undetected tumor. She also endorsed contact with her COVID +, asymptomatic grandson ~ 1 week prior to presentation, coincidental with the headache onset. Based on these symptoms, she was placed on strict COVID-19 precautions with appropriate isolation measures. Subsequent polymerase chain reaction (PCR) testing determined she was positive for SARS-CoV-2. The patient was taken for transcranial resection of her sellar mass on the day of presentation. She underwent a right frontoparietal craniotomy without complications. Pathology confirmed a null-cell adenoma. The headaches improved right after the surgical procedure and visual acuity in the right significantly improved from only light perception preoperatively to 20/50 and right hemianopsia after 1-month follow up. Postoperatively, the patient required substitutive treatment with hydrocortisone, levothyroxine, and desmopressin.

Patient #2. A 56-year-old obese male with a history of hypertension and hypothyroidism presented to an outside facility complaining of headache, approximately 1 week prior to arrival at our center. He was given analgesics, fluids and discharged home. Due to persistence of headache and the new onset of binocular diplopia, he presented to his primary care physician who ordered CT head revealing a sellar hemorrhagic mass. He was subsequently transferred to our tertiary care institution. On arrival, neurologic examination revealed decreased mental status and complete third and fourth cranial nerve palsies, although no visual deficits were objectively assessed given his altered mental status. These findings prompted evaluation with MRI that demonstrated a sellar hemorrhagic lesion with invasion of the right cavernous sinus. Further questioning revealed chills and myalgias starting 10 days prior to admission. PCR testing determined he was positive for SARS-CoV-2. The patient was taken for endonasal trans sphenoidal microscopic resection of his sellar mass on the day of admission. He was discharged home on postoperative day 2 with no evidence of hyponatremia or diabetes insipidus, although he required treatment with hydrocortisone and levothyroxine. Postoperative course was uneventful and neurologic exam at 6 weeks follow-up revealed complete resolution of the third and fourth cranial nerve palsy. Final pathology demonstrated necrotic tissue within a lactotroph-type pituitary adenoma, confirming the diagnosis of pituitary apoplexy.

Patient #3. A 52-year-old male with a past medical history of hypertension and obesity presented to the emergency department complaining of acute onset of headache, accompanied by one year of progressive loss of peripheral vision, initially on his left eye, followed after a few months by his right eye. He also endorsed decreased libido and inability to maintain an erection for approximately 2 years prior to presentation. He was evaluated by ophthalmology who documented bitemporal hemianopsia. These findings prompted obtaining an MRI brain with pituitary protocol revealing a sellar mass with a significant hemorrhagic component with sellar remodeling and upward displacement of the optic chiasm. Close follow up appointment 3 days later revealed increased intensity of headaches and no improvement of visual symptoms. He subsequently was scheduled for elective endoscopic trans sphenoidal resection of his sellar mass. Patient had preoperative pituitary labs demonstrating central hypothyroidism, hypogonadism, low IGF-1 and low-to-normal cortisol levels. Surgery was uneventful. Intraoperatively, a predominantly liquefied hemorrhagic mass was identified with necrotic tissue particularly along the posterior aspect of the sella which was markedly expanded. The day after the intervention the patient experienced respiratory symptoms consisting of cough and short of breath, accompanied by low grade fever and chills. This prompted screening for COVID, which revealed a positive result. Pathology confirmed a lactotroph pituitary adenoma. After surgery, he was placed on hydrocortisone therapy due to hypocortisolism and was discharged home on postoperative day 3 with no evidence of hyponatremia or diabetes insipidus. Post-operatively the patient made an excellent recovery with complete reversal of his visual disturbances.

Discussion

Our recent experience in three consecutive patients with pituitary apoplexy who all suffered from concomitant COVID-19 infection raises concern for a potential relationship between these two identities.

Although the exact mechanism of PA is not fully understood, it is generally accepted that it occurs as a consequence of an infarction or hemorrhagic infarction of the pituitary gland[10, 11]. From a pathophysiological perspective, SARS-Cov-2 has shown specific tropism to the central nervous system and utilizes angiotensin-converting enzyme 2 (ACE2) receptors on host cells for its internalization[12]. Once in the nervous system, SARS-Cov-2 induces downregulation of ACE2 receptors, which causes imbalance in oxidative stress, vasodilation, neuroinflammation, and thrombogenesis that may contribute to stroke pathophysiology of COVID-19 and hence, the development of PA in patients with pituitary adenomas[11].

Our observations are in line with mounting data pointing to neurologic manifestations in COVID-19 positive patients. There is accumulating evidence to suggest that SARS-CoV-2 targets the nervous system. Reported rates of stroke in patients with COVID-19 infection ranges between 0.9 and 5.7 percent[13, 14], while the incidence of cerebral thrombosis can be as high as 36 %[15]. In another study, of 32 critically ill patients with COVID-19, 8 (25%) had severe central nervous system involvement[16]. Stroke patients with COVID-19 infection were more likely to be younger and have higher admission National Institute of Health Stroke Scale (NIHSS) score[14]. Similarly, intracranial hemorrhage or cerebral microbleeds have been shown in up to 22% of critically ill patients[16]. Therefore, there exists a plausible biological mechanism that explains the possible role of COVID infection as a risk factor for developing PA.

Coexistence of PA and COVID-19 infection has been previously reported[17, 18]. The significance of this correlation is still unclear [17]. Similarly, Chan et al [18] reported another case of a patient with PA who also tested positive for COVID-19 infection, although in this case, pregnancy may have played an important role in the development of the pituitary infarction[19]. Following the Bradford-Hill criteria that assesses epidemiological evidence of causality between a cause and effect[20], what this works adds to the previous knowledge is a more robust strength of the association (largest series to date), consistency of the results (three consecutive patients in one neurosurgery department), and the absence of any relevant factor that predispose to PA (specificity). While several risk factors, including head trauma, intracranial hypertension, radiotherapy, pregnancy, or anticoagulation, have been described as the potential cause of hemorrhagic infarction of the pituitary gland[11, 21], none of these were found in any the three patients presented here. In addition, temporality is another principle to stablish causality that is met in our report of three consecutive cases. Two of our patients had a positive test demonstrating COVID infection within the month prior to admission for PA. The third patient tested positive after respiratory symptoms that were developed 4 days after he was diagnosed with PA. If considering the mean incubation time of SARS-Cov-2 is estimated to be 5 days, we can prompt that our third patient was likely already infected when he experienced symptoms relative to the pituitary infarction.

From the management perspective, it is worthwhile to highlight the importance of monitoring fluid and electrolyte balance and correction of pituitary hormone deficiencies[11]. Once the patient is stabilized, the surgical indication mostly depends on visual status. PA is generally considered a surgical emergency when associated with acute visual dereterioration[10, 11]. Interestingly, some patients have experimented

spontaneous visual improvement with conservative management using steroids[22, 23]. We attempted to opt for conservative management in one of our patients (patient #2), given the subacute progression of his visual symptoms. Nevertheless, the lack of visual improvement after a short interval of observation, prompted the need to proceed with surgical resection. The surgical intervention can be carried out through a transsphenoidal or a transcranial route[10, 11]. However, the increased risk of SARS-Covs-2 dissemination to healthcare workers during transsphenoidal surgery due to aerosolization of viral particles has led some centers to favor the transcranial route or even delay the intervention in non-emergent cases[24]. In our case, just in patient #1 we preferred the transcranial approach, given the lack of benefit in a patient with a large adenoma with suprasellar extension.

The present study has several limitations. Most importantly, its descriptive nature and the small selected sample size prevents from extracting definitive conclusions about the true incidence of PA in patients with COVID-19. However, we believe that our study provides relevant preliminary data regarding pituitary apoplexy in patients with COVID-19.

Conclusion

As in other neurological manifestations, COVID-19 positive patients may be at an increased risk of developing PA. While the exact mechanisms remain to be elucidated, it is possible that the ACE-2 receptors expressed in cerebrovascular endothelium plays an important role in the molecular mechanisms that induce changes of the vascular autoregulation and cerebral blood flow and predispose to infarction of the pituitary gland.

Declarations

Disclosure Funding: This study did not receive any funding relative to its elaboration.

Conflict of interest: The authors do not report any conflict of interest.

Ethical approval and informed consent (to participate and for publication): Informed consent and ethical approval were not deemed necessary by the local ethics in view of the design of the study (3-case series).

Availability of data and material (data transparency): This manuscript has not been previously published in whole or in part or submitted elsewhere for review.

Authors contribution: Conception and design of study: Rafael Martinez-Perez, Marcus Zachariah, Gustavo Luzardo; acquisition of data: Benjamin Carrol, Daniel Duran; analysis and/or interpretation of data: Rafael Martinez-Perez, Daniel Duran, James Neill; drafting the manuscript: Rafael Martinez-Perez, revising the manuscript critically for important intellectual content: Marcus Zachariah, Gustavo Luzardo; Approval of the version of the manuscript to be published: All the authors

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Figures

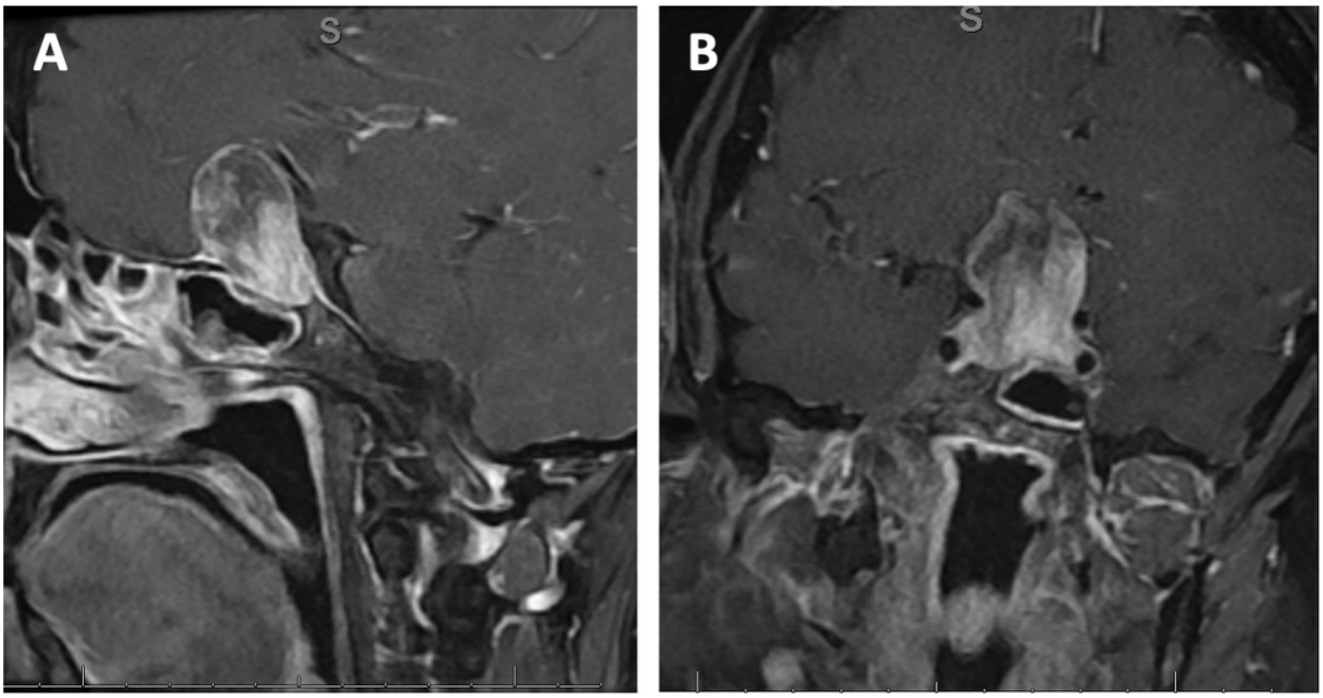

Figure 1

Patient #1. T1-weighted contrast-enhanced magnetic resonance imaging (Panels A (sagittal) and B (coronal) showed a 28 mm mixed hyperintense- hypointense sellar lesion, compatible with a pituitary adenoma with blood products in different stages of degradation

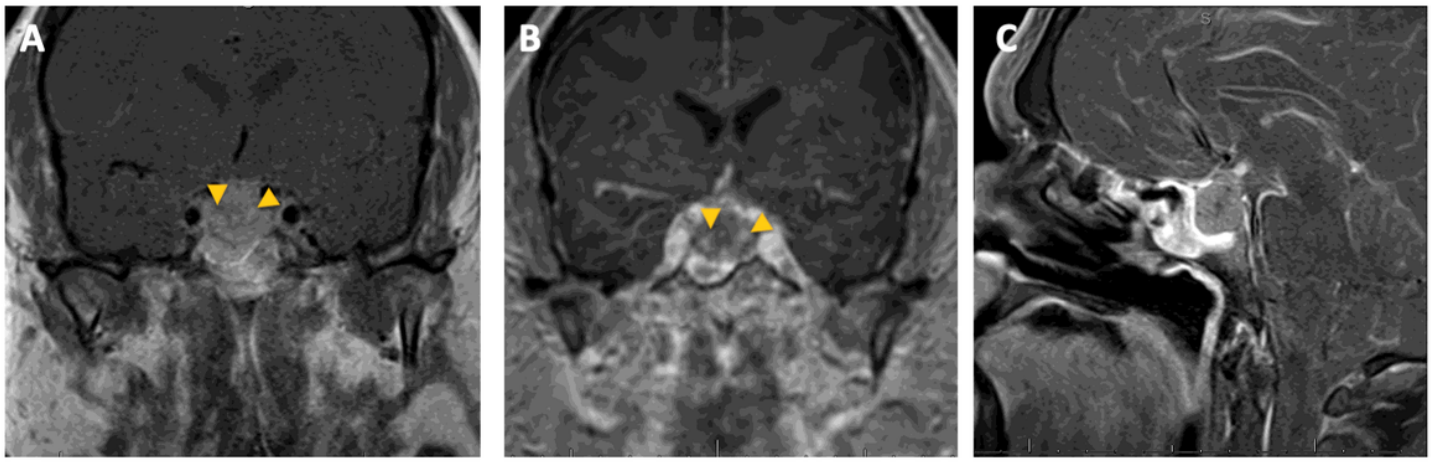

Figure 2

Patient #2. Preoperative magnetic resonance imaging showed a pituitary apoplexy (hemorrhage marked by arrowhead) in a macroadenoma with interval enlargement (18 mm) shown in T1 phase without (A) and with contrast (coronal -B- and sagittal view -C-).

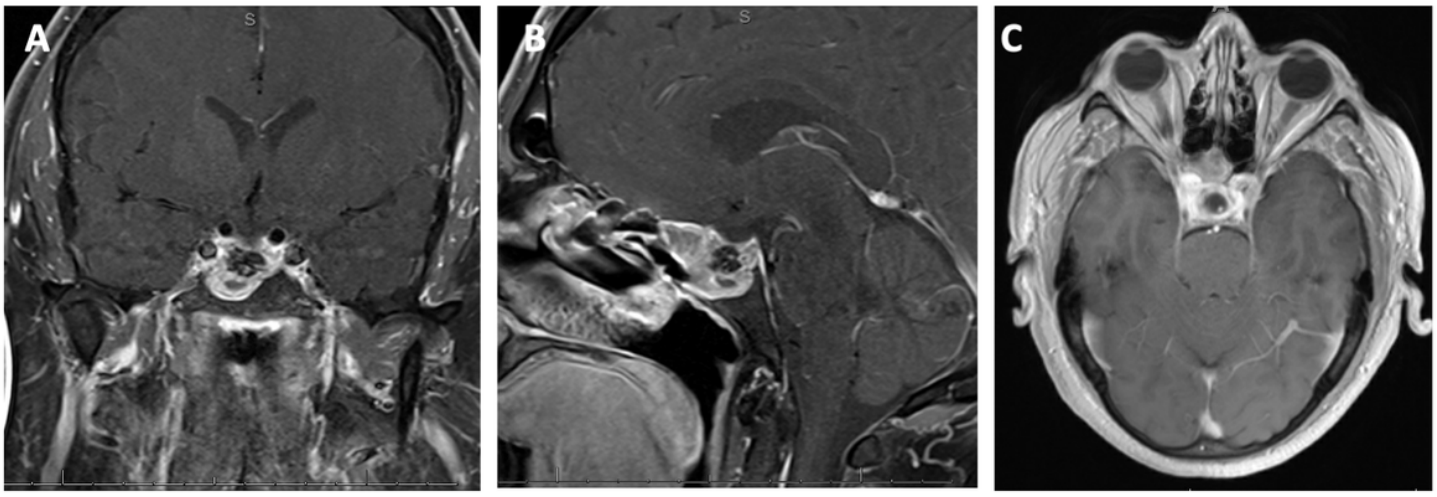

Figure 3

Patient #2. T1-weighted contrast-enhanced magnetic resonance imaging showing adequate decompression of the optic apparatus (Coronal -A-, sagittal -B-, and axial -C- views)

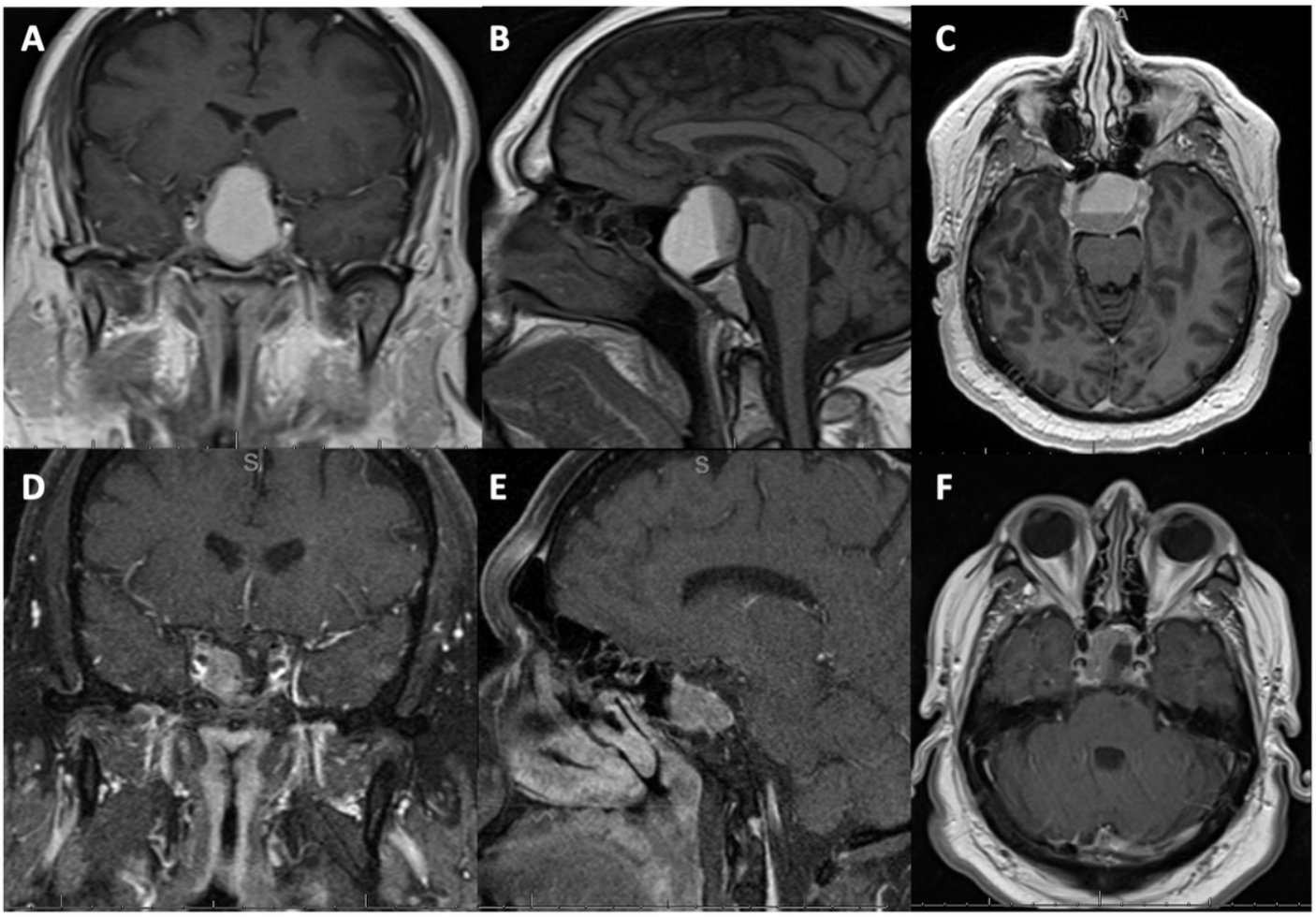

Figure 4

Patient #3. Preoperative T1-weigthed contrast-enhanced magnetic resonance imaging (A, B, and C) showed a sellar lesion with suprasellar extension and a T1-hyperintense fluid level, compatible with intratumoral subacute bleeding. Postoperative T1-weigthed contrast-enhanced magnetic resonance imaging demonstrated decompression of the optic chiasm and tumor residual extending into the right cavernous sinus.