Infarctive Apoplexy of Previously Healthy Pituitary Glands: A Small Case Series and Literature Review

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J Neurol Surg Rep 2023;84:e71–e79.

Abstract

Introduction We present two cases of suspected pituitary apoplexy found instead to be infarcted pituitary glands without histopathologic evidence of neoplastic cells, likely resulting from spontaneous infarction of previously healthy pituitary glands.

Case Presentations The first case is a 55-year-old man who presented with a pulsating headache, nausea, and several months of decreased libido, polyuria, and polydipsia. Magnetic resonance imaging (MRI) revealed a rim-enhancing sellar/suprasellar mass with evidence of recent hemorrhage on the right. Testosterone, follicle-stimulating hormone, and luteinizing hormone levels were suppressed. Analysis of the resected specimen showed fibrocollagenous tissue with evidence of old hemorrhage and microscopic focus of necrotic tissue. The second case is a 56-year-old man who presented with a throbbing headache, associated nausea, and 6 weeks of polyuria and polydipsia. Testosterone levels were found to be low, and 8-hour water deprivation test showed evidence for partial diabetes insipidus. MRI revealed a mass on the right side of the pituitary gland, with evidence of likely hemorrhage on the left. Analysis of the resected specimen showed necrotic tissue without neoplastic cells.

Conclusion When evaluating small pituitary lesions in patients presenting with indolent onset of pituitary insufficiency, there should be a high degree of suspicion for an infarcted pituitary gland.

Keywords
- pituitary apoplexy
- pituitary infarction
- infarctive apoplexy
- pituitary insufficiency
- necrotic pituitary

Introduction

Pituitary apoplexy is a rare and potentially life-threatening condition caused by either ischemia or hemorrhage of the pituitary gland. While the incidence of apoplexy within the pituitary has been shown to be variable due to many cases remaining undiagnosed, it has most often been reported to occur in the setting of pituitary adenomas. It has been reported in 1 to 26% of cases of pituitary adenomas, with some studies asserting that up to 82% of cases occur within nonfunctional adenomas.[1–3] In many cases, over 80% of patients by some reports, an apoplectic episode is the first presentation leading to discovery and diagnosis of pituitary adenomas.[4]

received
September 22, 2022
accepted
January 26, 2023

DOI https://doi.org/10.1055/s-0043-1770788.
ISSN 2193-6366.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Presentation of pituitary apoplexy ranges from potentially life-threatening, due to subarachnoid hemorrhage and acute cardiovascular collapse and resultant hemodynamic instability, to asymptomatic or subclinical apoplexy. Subclinical pituitary apoplexy, defined by intratumor hemorrhage and necrosis without clinical presentation of headache and other symptoms, is more common than classical apoplexy and occurs in up to 22% of pituitary tumor patients.[5] Classical pituitary apoplexy generally presents with an acute onset of symptoms. While the most frequently reported complaint is sudden onset of severe headache, other common manifestations include nausea, vomiting, visual impairment, ophthalmoplegia, and altered consciousness.[1] In addition to these clinical symptoms, apoplexy can also lead to pituitary insufficiency, resulting in loss of anterior and/or posterior pituitary hormones and a range of endocrinologic defects, such as adrenal insufficiency, diabetes insipidus (DI), hypothyroidism, and hypogonadotropic hypogonadism.[6]

Since pituitary apoplexy can be easily misdiagnosed, the use of proper diagnostic testing along with a thorough evaluation of clinical symptoms is required. Other conditions, such as bacterial meningitis or subarachnoid hemorrhage, may present with similar symptoms to pituitary apoplexy.[7] Since cerebrospinal fluid (CSF) analysis has provided little value in differentiating between these events, the use of computed tomography (CT) or magnetic resonance imaging (MRI) is required. While CT is superior in an acute setting within the first 12 hours of hemorrhage, MRI becomes superior after this window and provides more accurate diagnostic information about whether pituitary apoplexy is related to hemorrhage or infarction.[8] MRI can also be used to estimate the chronology of the bleed, with chronic apoplexy (>21 days) appearing as strong hypointensities on T1- and T2-weighted sequences.[9–11] However, examination of the pituitary mass after surgical resection remains the most accurate method in making a definitive diagnosis.

After a diagnosis is made, determining the most appropriate treatment method is critical. All patients must undergo an initial evaluation of pituitary gland function and be provided with supportive therapy to treat emergent electrolyte and fluid imbalances and hormonal deficiencies, particularly corticosteroids in the setting of adrenal insufficiency.[12] However, the use of surgical versus conservative management alone to treat pituitary apoplexy in an acute setting remains a topic of debate. This is largely due to the lack of large-scaled randomized control studies comparing outcomes of the two approaches. Patients who are clinically unstable or present with severe neurological, visual, or endocrine deficits generally require an urgent surgical approach for decompression and recovery. However, those who have more stable visual impairments, isolated cranial nerve palsies, or even some endocrine deficits can often be treated with a more conservative approach using conservative medical management with no decrease in quality of outcome compared with patients who undergo surgery.[7,13–15]

Few cases of pituitary apoplexy have been reported outside the context of pituitary adenomas, such as in peri- or postpartum women in the setting of hypovolemia.[16] Other factors that may predispose patients to pituitary apoplexy, with or without a preexisting adenoma, are generally related to prothrombotic events and alterations in vascular perfusion. These include hyper-/hypotension, anticoagulation therapy, clotting disorders, head trauma, angiographic procedures, and surgery, particularly that of cardiac and orthopaedic focus. Here, we present two unique cases of patients presenting with acute symptoms and imaging suggestive of pituitary adenoma apoplexy in the setting of chronic pituitary insufficiency found to have infarcted pituitary tissue on histopathologic analysis without evidence of neoplasm. The absence of neoplastic pituitary tissue on histopathologic analysis classically associated with pituitary apoplexy and indolent disease courses of both patients leads us to believe these cases are related to a rarer subset of apoplexy—infarctive apoplexy, likely of previously healthy pituitary glands.

Case Presentations

55-Year-Old Man with Hypogonadotropic Hypogonadism

The first case is a 55-year-old man with a past medical history of vitiligo since his early teens and hypertension, on metoprolol 50 mg orally twice daily, who presented to the emergency department (ED) at an outside hospital in January 2021 with 1 day of pulsating frontal headache with associated nausea and vomiting. He also reported several months of decreased libido, loss of morning erection, polyuria, polydipsia, hot and cold flashes, and insomnia. He denied visual disturbances, back pain, numbness, tingling, and difficulty walking. He denied other symptoms of gonadal dysregulation, such as decreased muscle mass and changes in testicular size and consistency. He also denied other symptoms of thyroid dysregulation, including anxiety, palpitations, constipation, and dry skin. He denied symptoms of growth hormone dysregulation, such as increase in hat, ring, or shoe size; increase in central adiposity; and cognitive decline. He also denied symptoms of adrenal dysregulation, such as proximal muscle weakness, thinning skin, hair loss, history of bone fractures, hypoglycemia, and lightheadedness. He denied any gynecomastia. His family history was negative for diseases of the pituitary gland and hypercalcemic syndromes but positive for hypertension in two siblings and his mother and for stroke in his mother. Neurological examination and ophthalmologic testing, including optical coherence tomography (OCT) and Humphrey visual field testing (HVF), were unremarkable.

MRI of the brain with and without contrast at the outside hospital at presentation revealed a rim-enhancing sellar/suprasellar mass measuring 2.2 cm × 1.8 cm × 2.2 cm (craniocaudal [CC] × anteroposterior [AP] × transverse [XT]) with evidence of recent hemorrhage on the right side of the lesion. Further workup at presentation (►**Table 1**) revealed morning cortisol levels were decreased, although this may have been attributed to a recent dexamethasone suppression test. Total testosterone and free testosterone were markedly decreased, in the setting of follicle-

Table 1 Summary of laboratory workup, including pituitary panel, for case 1

Laboratory value	January 22, 2021 (presentation)	March 10, 2021	April 20, 2021 (2 mo preresection)
Morning cortisol, mcg/dL (ref. 5.0–25.0)	1.6[a]	7.74	16.5–19.4
ACTH, pg/mL (ref. 10.0–60.0)		20.7	13.0
IGF-1, ng/mL (ref. 71.0–290.0)	275	123	58
FSH, mIU/mL (ref. 1.5–12.4)	7.5[c]		1.5[c]
LH, mIU/mL (ref. 1.7–8.6)	4.0[c]	1.1[c]	0.8[c]
Total testosterone, ng/dL (ref. >215)	37.6 (L)	17.0 (L)	
Free testosterone, pg/mL (ref. 7.2–24.0)	0.6 (L)	3.1 (L)	
Prolactin, ng/mL (ref. <15)	7.04–8.07	13.13	9.8
Growth hormone, ng/mL (ref. 0.03–2.47)	0.82–1.59		
TSH, U/L (ref. 0.47–6.9)	0.58[b]	0.69	0.07
Free T4, ng/dL (ref. 0.75–2.0)	1.5	0.72	1.1
Serum osmolality, mOsm/kg (ref. 275–295)	261–281		302

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid stimulating hormone; T4, thyroxine.
Note: L indicates the value is lower than the reference range.
[a]May be reflective of recent dexamethasone suppression test.
[b]Equivocal value, but warranting medical treatment.
[c]Expected to be elevated in response to low testosterone, values within reference range in this context indicate pituitary hypofunction.

stimulating hormone (FSH) and luteinizing hormone (LH) levels within reference ranges; the lack of compensatory elevation in FSH and LH levels in this context indicated pituitary hypofunction. Prolactin levels were within normal limits. Insulinlike growth factor 1 (IGF-1) levels were slightly elevated, and growth hormone, thyroid-stimulating hormone (TSH), and thyroxine (T4) levels were within normal limits. Other laboratory workup, including complete blood count and basic metabolic panel, was unremarkable. At this time, the patient was started on 30 mg oral hydrocortisone daily for possible adrenal insufficiency and 100 mcg oral levothyroxine daily for low to normal TSH levels. Surgery was not pursued at this time due to cardiac abnormalities warranting further workup. A multidisciplinary discussion in the setting of unremarkable neurological and ophthalmologic examination determined that in the meantime, the patient should be discharged with instructions for outpatient follow-up with serial surveillance imaging with further outpatient ophthalmologic, neurosurgical, and endocrinologic follow-up for symptoms of central hypogonadism and DI.

Repeat imaging 3 months after presentation, in April 2021, revealed a hypoenhancing lesion measuring 1.2 cm × 0.6 cm × 1.4 cm (CC × AP × XT) in an expanded left sella with the residual pituitary tissue and pituitary stalk deviated to the right (►**Fig. 1**). Repeat laboratory workup (►**Table 1**) conducted around this time revealed normal morning cortisol and adrenocorticotropic hormone (ACTH) levels. Total and bioavailable testosterone levels remained low, while FSH and LH remained within reference ranges.

Gross analysis of the resected specimen following uncomplicated transsphenoidal surgery (TSS) in June 2021, 5 months after presentation, showed a red-tan to yellow irregularly shaped mass. Histopathologic analysis revealed fibrocollagenous tissue with evidence of old hemorrhage and microscopic focus of necrotic tissue (►**Fig. 2**). The patient recovered well in the neurological intensive care unit after surgery and was discharged on postoperative day 2 without signs of postoperative DI or other complaints. After resection, the patient's hydrocortisone, metoprolol, and levothyroxine were discontinued. Postoperative MRI performed 4 months after resection revealed postoperative changes (►**Fig. 1**). As of the most recent follow-up in February 2022, the patient continues to do well with complete resolution of his symptoms and normal cortisol, TSH, and free T4 levels; his hypertension also continues to be managed nonmedically.

56-Year-Old Man with Hypogonadotropic Hypogonadism and Diabetes Insipidus

The second case is a 56-year-old man with a history of psoriatic arthritis, treated with 40 mg adalimumab injection every 2 weeks and 20 mg oral methotrexate weekly, and nonmedically managed hypertension who presented to the ED in March 2019 with 1 day of constant severe, throbbing, and nonradiating frontal headache, with associated photophobia, dizziness, lightheadedness, and nausea. He reported 6 weeks of polyuria and polydipsia, requiring him to drink approximately two gallons of water per day and to urinate every 15 minutes during the day and every 30 minutes overnight. He also reported a few months of occasional blurring of peripheral vision, difficulty walking, night sweats, intermittent hot flashes, and profound fatigue. He denied heat/cold intolerance, unexpected weight changes, and galactorrhea. He also denied any inciting event or relief of symptoms with naproxen or Excedrin. His family history is

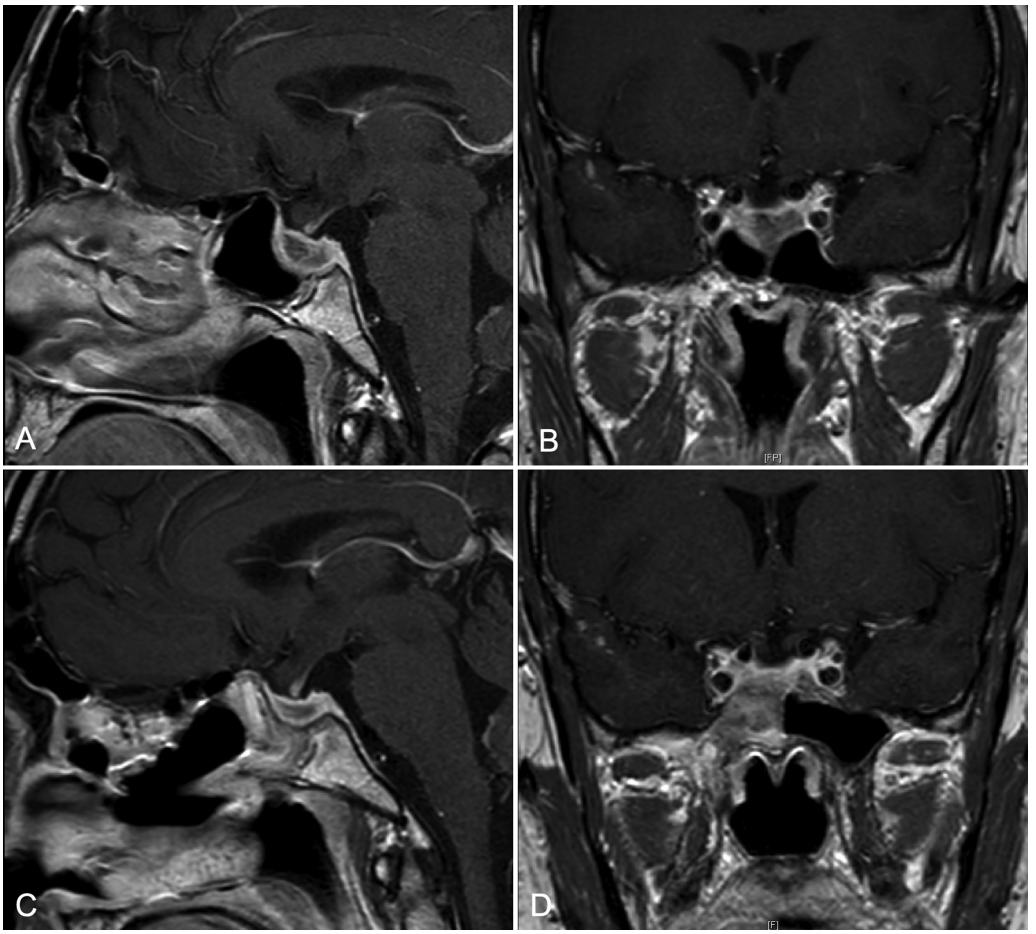

Fig. 1 Case 1: Pre- and postresection magnetic resonance imaging (MRI) of the sella. Preoperative T1-weighted contrast-enhanced MRI in (**A**) coronal plane and (**B**) sagittal plane demonstrating hypoenhancing lesion in the left sella with evidence of hemorrhage on the right side of the lesion and residual pituitary tissue and stalk deviated to the right. Postoperative T1-weighted contrast enhanced MRI in (**C**) coronal plane and (**D**) sagittal plane demonstrating postoperative change in the setting of complete resection of the lesion.

notable for hypertension in his brother and cerebral aneurysm in his father. He is a never smoker and denied any alcohol or recreational drug use. Physical examination at presentation was notable for blood pressure of 157/92 mm Hg and body mass index (BMI) of 30.85 km/m^2. Neurological and ophthalmologic examinations, including OCT and HVF, were unremarkable. CT of the head without contrast at presentation showed a hyperdense sellar/suprasellar mass

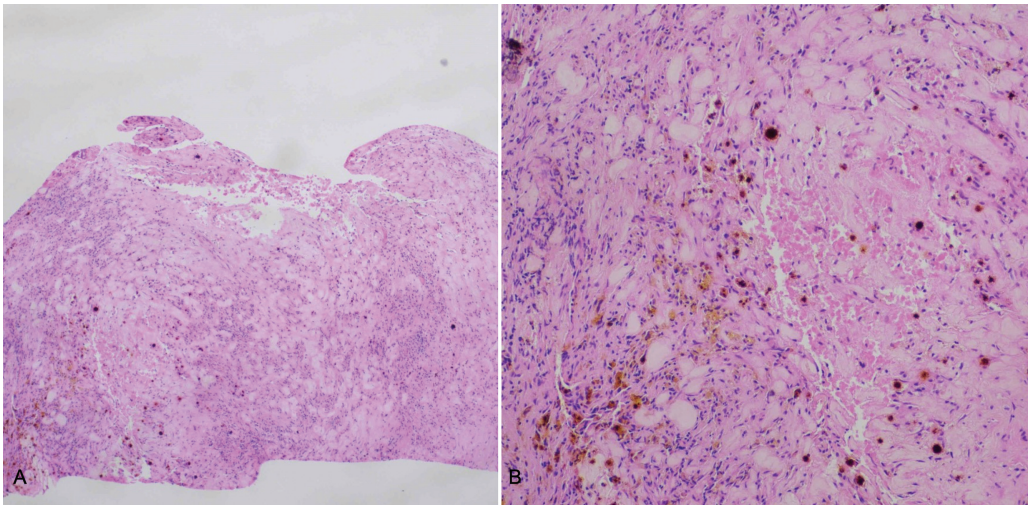

Fig. 2 Case 1: Histopathologic analysis of resected pituitary specimen. (**A**) 100x magnification and (**B**) 200x magnification demonstrating fibrocollagenous tissue with evidence of old hemorrhage and microscopic focus of necrotic tissue without evidence of neoplastic cells.

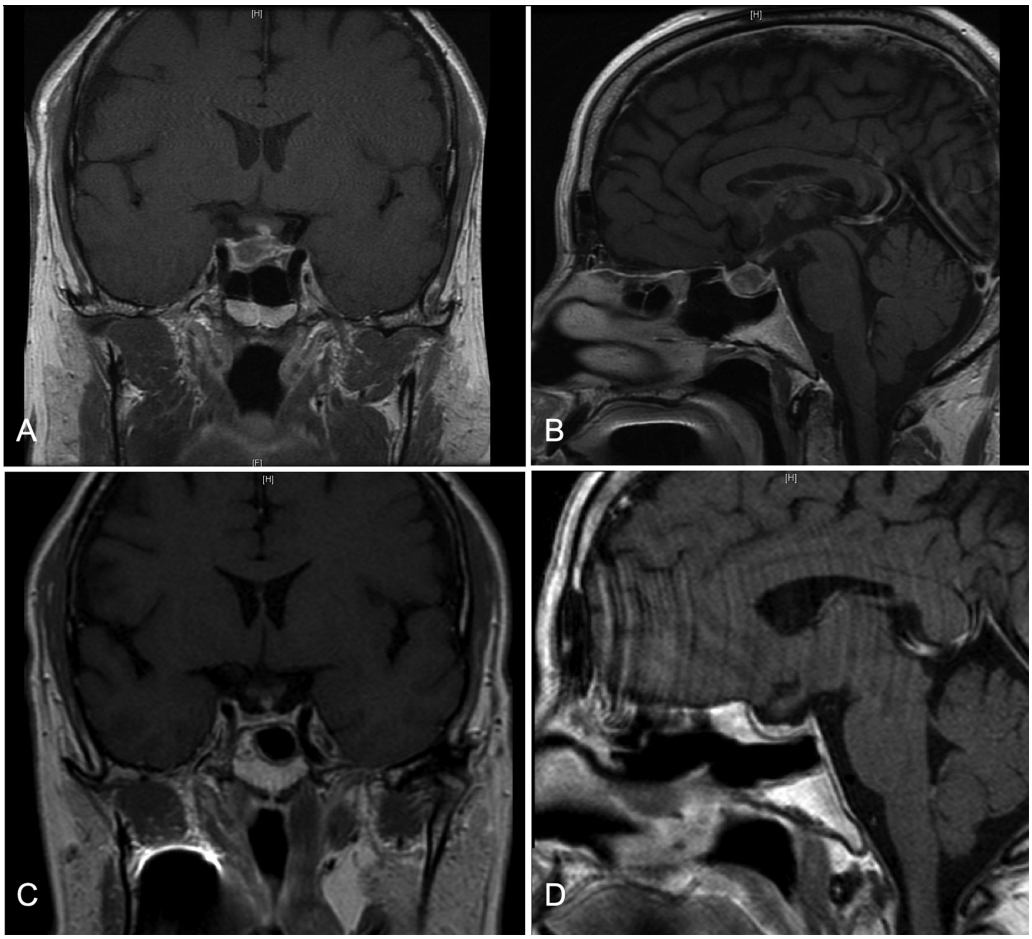

Fig. 3 Case 2: Pre- and postresection magnetic resonance imaging (MRI) of the brain. Preoperative T1-weighted fluid attenuated inversion recovery (FLAIR) contrast-enhanced MRI in (**A**) coronal plane and (**B**) sagittal plane demonstrating soft-tissue mass in the right pituitary gland and likely hemorrhage in the left pituitary gland with infundibulum deviated to the left. Postoperative T1-weighted contrast-enhanced MRI in (**C**) coronal plane and (**D**) sagittal plane demonstrating postoperative change in the setting of complete resection of the lesion.

1.7 cm in greatest diameter (CC). Surgical resection was not possible at this time due to patient compliance issues, but the patient was instructed to follow up for further surveillance and workup by neurosurgery, ophthalmology, and endocrinology in an outpatient setting.

MRI performed 2 months after presentation revealed a soft-tissue mass extending from just left of the midline of the pituitary gland through to the right side measuring 1.0 × 0.8 × 1.0 cm (CC × AP × XT) in greatest dimensions, displacing the slightly thickened infundibulum to the left; the left half of the pituitary showed marked T2 hypointensities and mixed T1 intensity without definite enhancement most likely representing chronic hemorrhage (►**Fig. 3**). Laboratory workup performed at this time (►**Table 2**) revealed low total testosterone and free testosterone levels, as well as equivocally low cortisol levels and atypically low prolactin, IGF-1, and free α subunit levels. Serum osmolality was slightly elevated, and urine creatinine and urine sodium levels suggested dilute urine. Other laboratory workup, including TSH, T4, ACTH, FSH, and LH levels, was within normal limits.

Repeat laboratory workup 3 months after presentation (►**Table 2**) revealed persistently equivocally low IGF-1, cortisol, free α subunit, and prolactin levels. Total and free midmorning testosterone levels remained low; while expected to be elevated in this context, LH and FSH levels remained within reference ranges, suggesting central hypogonadism. At this time, stress dose of hydrocortisone, consisting of 10 mg orally each morning and 5 mg orally each evening, was initiated perioperatively due to equivocal cortisol in the setting of pituitary compromise. An 8-hour water deprivation test performed at this time showed evidence for partial DI, and the patient was started on 0.05 mg of oral DDAVP (desmopressin acetate) twice daily.

The patient underwent uncomplicated TSS for resection of the sellar mass in June 2019, 3 months after presentation, which revealed an irregularly shaped tan-pink mass on gross analysis. Histopathologic analysis of the resected specimen showed infarcted, necrotic tissue without evidence of neoplastic cells (►**Fig. 4**). The patient required maintenance of desmopressin for treatment of DI while hospitalized. He otherwise recovered well as expected in the neurological intensive care unit after surgery and was discharged on postoperative day 6, with instructions to continue taking 0.05 mg oral DDVAP twice daily. Follow-up laboratory tests obtained 3 months after resection (►**Table 2**) revealed persistently low cortisol levels, after holding evening and morning

Table 2 Summary of laboratory workup, including pituitary panel, for case 2

Laboratory value	May 7, 2019 (2 mo after presentation)	June 5, 2019	September 25, 2019 (3 mo after resection)	March 5, 2021	July 13, 2021
Mid-morning cortisol, mcg/dL (ref. 5.0–25.0)	7.4	7.0[a]	4.6 (L)		6.4
ACTH, pg/mL (ref. 10.0–60.0)	27.0			17	26
IGF-1, ng/mL (ref. 71.0–290.0)	43.0 (L)	46.0[a]		56	
FSH, mIU/mL (ref. 1.5–12.4)	2.6[b]	3.8[b]	3.3[b]	3.1[b]	2.5[b]
LH, mIU/mL (1.7–8.6)	3.0[b]	3.5[b]	2.7[b]	1.4[b]	1.3[b]
Total testosterone, ng/dL (ref. >215)	180 (L)	186 (L)	194 (L)	125 (L)	98 (L)
Free testosterone, pg/mL (35.0–155)	25.9 (L)	28.3 (L)		26.9 (L)	21.8 (L)
Prolactin, ng/mL (ref. <15)	<5 (L)	5.2[a]		<5 (L)	
Free α subunit, ng/mL (0.1–0.5)	<0.1 (L)	<0.1 (L)			
TSH, mcU/mL (ref. 0.4–4.6)	1.5	2.8		1.46	
Free T4, ng/dL (ref. 0.75–2.0)	0.9	0.9		1.0	
Serum osmolality, mOsm/kg (275–295)	297	288–306[a]		296	
Urine creatinine, mg/dL (ref. 20–320)	42.3 (L)				
Urine sodium, mEq/L (ref. >20)	24.0 (L)				
Urine osmolality, mOsm/kg (300–1,300)		217 (L)			

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; IGF-1, insulinlike growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; T4, thyroxine.
Note: L indicates the value is lower than the reference range.
[a]Equivocal, but warranting medical treatment.
[b]Expected to be elevated in response to low testosterone, values within reference range in this context indicate pituitary hypofunction.

doses of hydrocortisone. Despite persistently low total testosterone levels, replacement therapy was not initiated due to absence of any change to the patient's sexual function or energy levels. Postoperative MRI performed 5 months after resection revealed postoperative changes (►**Fig. 3**).

Thirteen months after resection, DDVAP was discontinued due to resolution of polyuria and polydipsia in the setting of consistently normal urine osmolality. Two years after resection, in July 2021, laboratory workup revealed persistently markedly low total testosterone and free testosterone levels in the setting of normal FSH and LH levels (►**Table 2**). Testosterone replacement therapy, in the form of 150-mg injections every 2 weeks, was then initiated due to worsening hypogonadotropic hypogonadism. Cortisol levels at this time began normalizing, and the patient remains on the same maintenance dose of oral hydrocortisone, 10 mg daily during the day and 5 mg nightly. The patient is currently doing well without complaints on this hormone replacement regimen as of last follow-up in November 2021.

Discussion

In this small series, we believe we are describing a rare subset of infarctive apoplexy of potentially previously healthy pituitary glands. Typically, pituitary apoplexy is an acute ischemic infarction or hemorrhage of the pituitary gland.

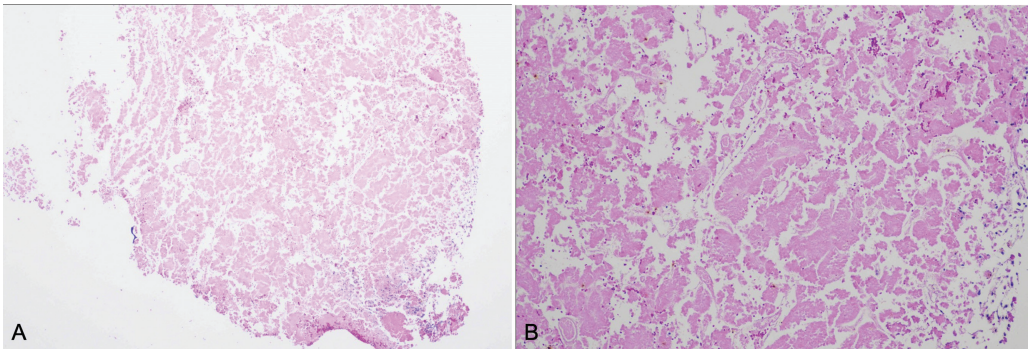

Fig. 4 Case 2: Histopathologic analysis of resected pituitary specimen. (**A**) 100x magnification and (**B**) 200x magnification demonstrating necrotic tissue without evidence of neoplastic cells.

First reported in 1898 by Bailey[17] and defined in 1950 by Brougham et al,[18] pituitary apoplexy most frequently involves an adenoma.[7] However, cases also occur in the setting of a nonadenomatous or normal pituitary gland during pregnancy.[16] Regardless, it is well established that in nonpregnancy settings, an adenoma or sellar mass is identified after a pituitary apoplexy event; in fact, apoplexy can often be the first presentation of pituitary adenomas. There are also cases of asymptomatic ischemic or hemorrhagic pituitary adenoma apoplexy termed subclinical pituitary apoplexy.[19,20] The two cases described in this study were found to lack the typical adenomatous or neoplastic pituitary tissue classically seen in cases of pituitary apoplexy, thus distinguishing them from such cases.

In classical pituitary apoplexy, patients most frequently present with sudden onset headache, usually located retroorbitally. Other common manifestations include nausea, vomiting, altered visual fields or visual acuity, altered consciousness, and symptoms of pituitary insufficiency. Hypogonadotropic hypogonadism is one of the most common endocrine deficiencies observed, with DI being far less common.[21] The two cases described in this study also presented with similar symptoms of sudden-onset headaches associated with nausea and vomiting. They also presented with other common signs and symptoms, such as visual changes and pituitary insufficiency—hypogonadotropic hypogonadism, polyuria, and polydipsia. Imaging findings, including rim enhancement and T1 and T2 hypointensity of and within the masses, and laboratory hormonal assays were also consistent with a diagnosis of pituitary apoplexy. However, typically, headache is the acute presenting symptom followed by subacute or chronic pituitary insufficiency; in both cases presented here, an acute headache was preceded by chronic symptoms of pituitary insufficiency. This chronology may be due to the increased pressure within the sella due to mass effect exerted by the expanding necrotic tissue, long after pituitary function has declined. Most importantly, pathology results of the resected specimens showed fibrocollagenous or necrotic tissue without any evidence of neoplasm. This is quite interesting considering the proposed pathophysiology behind hemorrhage, or less frequently infarction, of the pituitary gland in the setting of an adenoma.

The pituitary gland is supplied by a capillary network known as the hypophysial portal system, which originates from the hypothalamus and superior and inferior hypophysial arteries. In pituitary adenomas, vascularization is provided mainly by a direct arterial blood supply rather than a portal system.[22–25] Pituitary adenomas have been shown to have a reduced microvasculature compared with the normal pituitary gland, which may explain the vulnerability of these tumors to apoplexy when there are alterations in perfusion.[26] It is believed that pituitary adenomas are prone to bleeding and infarction for several reasons: the unique, rich vascular structure, outgrowth of the blood supply, or ischemia secondary to vascular compression from an expanding mass.[27,28] Pituitary adenomas are also known to have microvasculature changes that lead to their increased susceptibility for hemorrhage.[29,30] These changes that make pituitary adenomas more susceptible to hemorrhagic or infarction events are typically not present in normal pituitary glands. In both cases presented here, the patients were noted to have enlarged pituitary glands, each with a greatest diameter of approximately 2 cm, which is more than twice the size of normal pituitary glands. Pituitary hyperplasia due to low levels of circulating hormones, such as thyroid hormone, as well as due to physiologic adaptations to pregnancy in other cases, may also disrupt this delicate microvasculature and increase susceptibility to apoplexy. Thus, it is possible that a similar pathophysiology related to disruptions in normal perfusion drives both classical pituitary apoplexy and spontaneous pituitary infarction in these two patients with assumed previously healthy but enlarged pituitary glands. The exact reasons behind the enlarged pituitary glands presented here, however, remain unclear. Interestingly, both patients were also noted to have hypertension, which has been previously established as a precipitating factor for pituitary apoplexy due to altered vascular perfusion of the gland.[31,32]

We believe these cases are distinct from classical hemorrhagic pituitary apoplexy and may instead belong to a rarer class of apoplexy—infarctive pituitary apoplexy. The two subsets of infarctive apoplexy previously described in other small case series, ischemic pituitary apoplexy and coagulative necrotic pituitary apoplexy, are defined by large areas of acellular coagulative necrosis, and immunohistochemical staining may or may not reveal the presence of residual neoplastic cells in these cases.[33,34] While data are limited, these entities have been shown to be pathophysiologically distinct from hemorrhagic apoplexy, the most common type of apoplexy, and present with a more indolent subacute or chronic course of symptom onset, including cranial nerve palsies, endocrine dysfunction, and visual disturbances.[33,34] Our patients are similar to these patients due to their indolent onset of symptoms of endocrine dysfunction and histopathologic findings of large centers of necrosis. They, however, appear to be distinguished by lack of residual neoplastic cells on immunohistochemical analysis that has been described in some previous cases; the reason for this could be because extensive necrosis destroyed any identifiable adenoma cells or because the pituitary glands were previously healthy with no adenomatous cells ever present. For these reasons, we believe we are describing a rare subset of apoplexy, defined by the spontaneous infarction of likely previously healthy pituitary glands, and resultant indolent onset of pituitary insufficiency.

Although we believe they represent a distinct entity, cases of infarctive pituitary glands should be managed similarly to cases of moderate to severe classical pituitary apoplexy presenting with worsening endocrine dysfunction and visual disturbances. While in some stable cases of classical pituitary apoplexy presenting with isolated deficits, medical management may be sufficient, surgical resection of the necrotic tissue was necessary for at least partial resolution of endocrine dysfunction in both cases of infarctive pituitary gland presented here. Previous reports indicate resolution of

preoperative DI within 1 year of TSS, which is similar to the outcome of the second case presented here.[34] This resolution of endocrine dysfunction is likely due to alleviation of the mass effect on the residual gland and stalk. However, as many as 80% of patients with pituitary apoplexy require some form of long-term hormone therapy, with corticosteroids and sex hormones being most commonly required[21]; this combination of long-term hormone therapy was actually observed in the second case presented here.

Some small previous studies report no difference in outcome between patients with pituitary apoplexy who underwent surgical resection within 1 week of presentation and those who underwent resection after 1 week.[34] Similarly, it is worth noting that in our series, more rapid surgical intervention did not prevent the need for long-term hormone replacement therapy in the second case. Interestingly, patients with lower prolactin levels at presentation, due to increased sellar pressure, have been found to be less likely to recover from endocrine hyposecretion following decompressive surgery for pituitary apoplexy, which was corroborated in this series.[35] While more studies are needed to investigate these relationships, the authors still recommend the threshold for surgical intervention in such cases be low to provide optimal chances for decompression and deficit reversal. This is because the indolent onset of symptoms in cases of infarctive pituitary apoplexy compared with classical apoplexy may delay proper surgical intervention and lead to irreversible deficits. Therefore, clinicians should be aware of this unique, albeit rare, disease process to accurately diagnose patients and potentially improve patient outcomes.

Conclusion

This report illustrates two cases of rarely described infarctive pituitary apoplexy, differentiated from classical apoplexy by the spontaneous infarction of previously normal pituitary glands and resultant indolent onset of pituitary insufficiency. Therefore, when evaluating small pituitary lesions in patients presenting with indolent onset of pituitary insufficiency, versus the acute onset of symptoms caused by classical hemorrhagic pituitary apoplexy, there should be a high degree of suspicion for the spontaneous infarction of an enlarged, previously healthy pituitary gland.

Conflict of Interest
None declared.

References

1 Capatina C, Inder W, Karavitaki N, Wass JA. Management of endocrine disease: pituitary tumour apoplexy. Eur J Endocrinol 2015;172(05):R179–R190
2 Mohr G, Hardy J. Hemorrhage, necrosis, and apoplexy in pituitary adenomas. Surg Neurol 1982;18(03):181–189
3 Mohanty S, Tandon PN, Banerji AK, Prakash B. Haemorrhage into pituitary adenomas. J Neurol Neurosurg Psychiatry 1977;40(10):987–991
4 Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. J Neurol Neurosurg Psychiatry 2001;71(04):542–545
5 Garg MK, Pathak HC, Singh G. Subclinical pituitary apoplexy with preserved pituitary functions. Indian J Endocrinol Metab 2014;18(01):122–123
6 Pyrgelis ES, Mavridis I, Meliou M. Presenting symptoms of pituitary apoplexy. J Neurol Surg A Cent Eur Neurosurg 2018;79(01):52–59
7 Nawar RN, AbdelMannan D, Selman WR, Arafah BM. Pituitary tumor apoplexy: a review. J Intensive Care Med 2008;23(02):75–90
8 Semple PL, Jane JA, Lopes MB, Laws ER. Pituitary apoplexy: correlation between magnetic resonance imaging and histopathological results. J Neurosurg 2008;108(05):909–915
9 Boellis A, di Napoli A, Romano A, Bozzao A. Pituitary apoplexy: an update on clinical and imaging features. Insights Imaging 2014;5(06):753–762
10 Bradley WG Jr. MR appearance of hemorrhage in the brain. Radiology 1993;189(01):15–26
11 Hardy PA, Kucharczyk W, Henkelman RM. Cause of signal loss in MR images of old hemorrhagic lesions. Radiology 1990;174(02):549–555
12 Chanson P, Lepeintre JF, Ducreux D. Management of pituitary apoplexy. Expert Opin Pharmacother 2004;5(06):1287–1298
13 Ayuk J, McGregor EJ, Mitchell RD, Gittoes NJ. Acute management of pituitary apoplexy: surgery or conservative management? Clin Endocrinol (Oxf) 2004;61(06):747–752
14 Mohindra S, Kovai P, Chhabra R. Fatal bilateral ACA territory infarcts after pituitary apoplexy: a case report and literature review. Skull Base 2010;20(04):285–288
15 Gruber A, Clayton J, Kumar S, Robertson I, Howlett TA, Mansell P. Pituitary apoplexy: retrospective review of 30 patients—is surgical intervention always necessary? Br J Neurosurg 2006;20(06):379–385
16 Grand'Maison S, Weber F, Bédard MJ, Mahone M, Godbout A. Pituitary apoplexy in pregnancy: a case series and literature review. Obstet Med 2015;8(04):177–183
17 Bailey P. Pathological report of a case of acromegaly with especial reference to the lesions in the hypophysis cerebri and in the thyroid gland; and a case of hemorrhage into the pituitary. Philadelphia Med J. 1898;1:789–792
18 Brougham M, Heusner AP, Adams RD. Acute degenerative changes in adenomas of the pituitary body: with special reference to pituitary apoplexy. J Neurosurg 1950;7(05):421–439
19 Findling JW, Tyrrell JB, Aron DC, Fitzgerald PA, Wilson CB, Forsham PH. Silent pituitary apoplexy: subclinical infarction of an adrenocorticotropin-producing pituitary adenoma. J Clin Endocrinol Metab 1981;52(01):95–97
20 Onesti ST, Wisniewski T, Post KD. Clinical versus subclinical pituitary apoplexy: presentation, surgical management, and outcome in 21 patients. Neurosurgery 1990;26(06):980–986
21 Ranabir S, Baruah MP. Pituitary apoplexy. Indian J Endocrinol Metab 2011;15(Suppl 3):S188–S196
22 Semple PL, De Villiers JC, Bowen RM, Lopes MB, Laws ER Jr. Pituitary apoplexy: do histological features influence the clinical presentation and outcome? J Neurosurg 2006;104(06):931–937
23 Gorczyca W, Hardy J. Microadenomas of the human pituitary and their vascularization. Neurosurgery 1988;22(1, Pt 1):1–6
24 Flerkó B Fourth Geoffrey Harris Memorial Lecture: the hypophysial portal circulation today. Neuroendocrinology 1980;30(01):56–63
25 Briet C, Salenave S, Bonneville J-F, Laws ER, Chanson P. Pituitary apoplexy. Endocr Rev 2015;36(06):622–645
26 Oldfield EH, Merrill MJ. Apoplexy of pituitary adenomas: the perfect storm. J Neurosurg 2015;122(06):1444–1449
27 Rolih CA, Ober KP. Pituitary apoplexy. Endocrinol Metab Clin North Am 1993;22(02):291–302
28 Rovit RL, Fein JM. Pituitary apoplexy: a review and reappraisal. J Neurosurg 1972;37(03):280–288

29 Di Ieva A, Weckman A, Di Michele J, et al. Microvascular morphometrics of the hypophysis and pituitary tumors: from bench to operating theatre. Microvasc Res 2013;89:7–14
30 Hirano A, Tomiyasu U, Zimmerman HM. The fine structure of blood vessels in chromophobe adenoma. Acta Neuropathol 1972; 22(03):200–207
31 Reid RL, Quigley ME, Yen SS. Pituitary apoplexy. A review. Arch Neurol 1985;42(07):712–719
32 Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf) 1999;51(02):181–188
33 Wang Z, Gao L, Wang W, et al. Coagulative necrotic pituitary adenoma apoplexy: a retrospective study of 21 cases from a large pituitary center in China. Pituitary 2019;22(01): 13–28
34 Zhu Q, Liang Y, Fan Z, et al. Ischemic infarction of pituitary apoplexy: a retrospective study of 46 cases from a single tertiary center. Front Neurosci 2022;15:808111
35 Zayour DH, Selman WR, Arafah BM. Extreme elevation of intrasellar pressure in patients with pituitary tumor apoplexy: relation to pituitary function. J Clin Endocrinol Metab 2004;89(11): 5649–5654