Spontaneous Regression of Pituitary Adenomas: Illustrative Case and Systematic Review

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ABSTRACT

INTRODUCTION

Spontaneous regression of pituitary adenomas is a rare occurrence that is thought to be due to pituitary apoplexy. We would like to review the demograhic data, imaging findings, and neurologic, endocrinologic, and radiologic outcomes of patients who exhibited this unusual phenomenon.

METHODS

We present a case of non-functioning pituitary adenoma (NFPA) in a 66-year-old man that underwent spontaneous regression. We also performed a systematic literature review on cases of pituitary adenomas that exhibited spontaneous regression, in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS

There have been only 27 reported cases of spontaneous regression observed in all pituitary adenomas, 16 of which are NFPAs. Headache was the most common symptom while decreased visual acuity and oculomotor nerve palsy were the most common sign. Pituitary hemorrhage was seen in two-thirds of cases, while findings suggestive of pituitary infarct, such as enhancement of the sphenoid sinus mucosa. were seen in one-third. Complete radiographic remission was observed in 62% of cases, with an 11% recurrence rate seen at least two years after the initial imaging. Neurologic recovery was reported in 88% and endocrinologic recovery from hypopituitarism was 40%.

CONCLUSION

Most patients exhibited neurologic and endocrinologic improvement concomitant with the regression of the pituitary adenoma. However, these tumors may recur; thus, regular and long-term neuro-ophthalmologic and radiologic follow-up is advised.

Key words: *Pituitary adenoma, spontaneous regression, spontaneous resolution*

INTRODUCTION

Pituitary adenomas are the most common sellar lesion and third most common intracranial tumor in adults.[1] These tumors occur with a mean prevalence of 89.1 cases / 100,000 population per year.[2] They can be functioning or non-functioning.[2] Prolactinomas are the most common subtype among pituitary adenomas, followed by non-functioning adenomas (NFPAs).[3]

List of Abbreviations

CT	Computed tomography
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
SIADH	Syndrome of inappropriate anti-diuretic hormone production
FT3	Free T3 (Thyroid hormone)
FT4	Free T4 (Thyroid hormone)

Symptomatic pituitary adenomas almost always require treatment, but there have been rare cases of spontaneous regression or resolution.[4–26] Pituitary apoplexy is cited as

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the most likely explanation in more than half of these cases.[4–9,11–14,17–19,21,22,24,26]

We would like to report an unusual case of spontaneous regression of a pituitary macroadenoma in a 66-year-old patient. To our knowledge, there have only been 27 reported cases of spontaneous regression observed in all pituitary adenomas, and 16 cases in NFPAs. This would be the 28th case overall and 17th NFPA reported in the literature. We also performed a systematic review of the literature to glean more knowledge about this rare phenomenon.

CASE REPORT

A 66-year-old man presented with a one-year history of progressive blurring of vision, diplopia, and numbness at the left forehead. Past medical history is significant for diabetes, hypertension, and dyslipidemia. On examination, the patient had a visual acuity of 20/100 on the right and 20/200 on the left. He had bitemporal hemianopsia on confrontation visual field testing, which was also documented by visual perimetry. He also had left lateral rectus palsy and sensory deficit of 30% at the left V1 distribution. Contrast-enhanced cranial MRI revealed a 2.1 x 2.3 x 2.08cm sellar-suprasellar tumor with a widened sella, left cavernous sinus extension, and chiasmatic compression. The tumor was isointense on both T1 and T2 sequences, with a focus of hyperintensity on both T1 and T2 (Figure 1). Hormonal panel revealed low FT3 and FT4, and normal thyroid-stimulating hormone, cortisol, and prolactin levels. The patient was started on thyroid hormone replacement therapy, but aside from this, he was not given any other new medication. He was also scheduled for transsphenoidal tumor excision but the operation was not performed immediately due to the long queue for surgery.

When the patient was admitted for surgery, 4 months after the initial consult, his visual acuity had improved to 20/50 bilaterally, and his bitemporal visual field cuts and craniopathies had resolved. Repeat cranial imaging showed marked regression of the sellar-suprasellar tumor (Figure 2). Surgery was deferred and the patient was sent home on close outpatient follow-up.

One year after the initial consult, the patient's visual acuity had improved to 20/20-1 bilaterally, with no visual field cuts and no craniopathies. His thyroid function tests remained low, and he continued thyroid replacement therapy.

MATERIALS AND METHODS

We conducted our systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[27]

Criteria for considering studies for review

We considered case reports, case series, and prospective and retrospective cohort studies in our review. We included studies that reported on patients with pituitary masses or tumors that spontaneously resolved. Spontaneous resolution was defined as regression, disappearance, or decrease in size of a pituitary tumor without any medical and/or surgical interventions. Relevant outcomes included improvement of patients' symptoms and normalization of hormone levels.

We excluded articles wherein patients were given any medication known to treat pituitary adenomas, such as bromocriptine, cabergoline, and octreotide. We also excluded microadenomas (tumors <10 mm in diameter), studies with no imaging documentation of tumor regression, and cases wherein surgery or biopsy of the tumor was performed prior to the regression of the lesion.

Search methods for identification of studies and selection of studies We searched scientific databases Medline by Pubmed, CENTRAL by Cochrane, Scopus, EBSCOHOST, and ClinicalTrials.gov from inception until September 2022. We used the following search terms: [("Pituitary mass" or "pituitary tumor" or "pituitary adenoma" or "pituitary neoplasm") and (MRI or "magnetic resonance imaging" or neuroimaging) and

Figure 1. T2-weighted (A) and contrast-enhanced T1-weighted (B, C) cranial MRI showed a 2.1 x 2.3 x 2.08 cm sellar-suprasellar tumor with a widened sella, cavernous sinus extension on the left, and chiasmatic

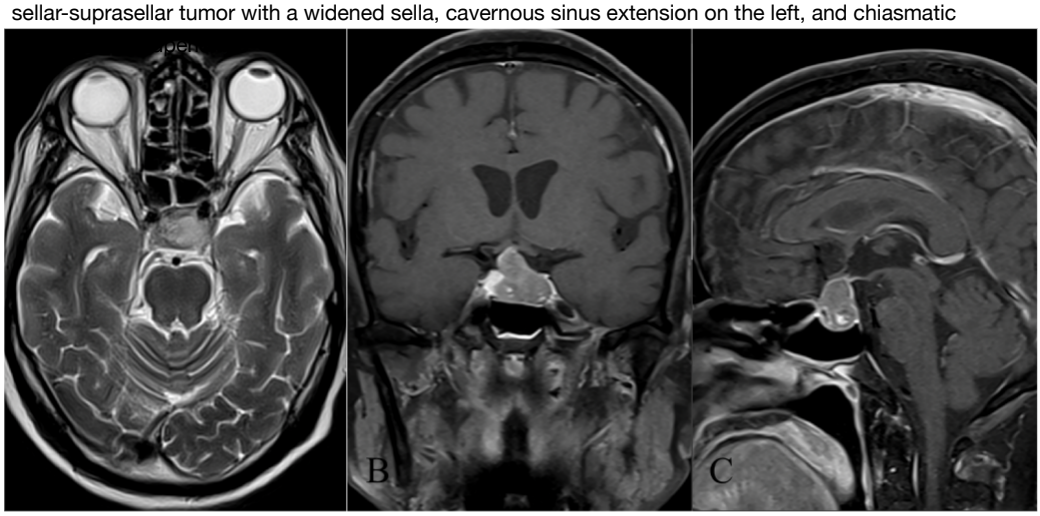
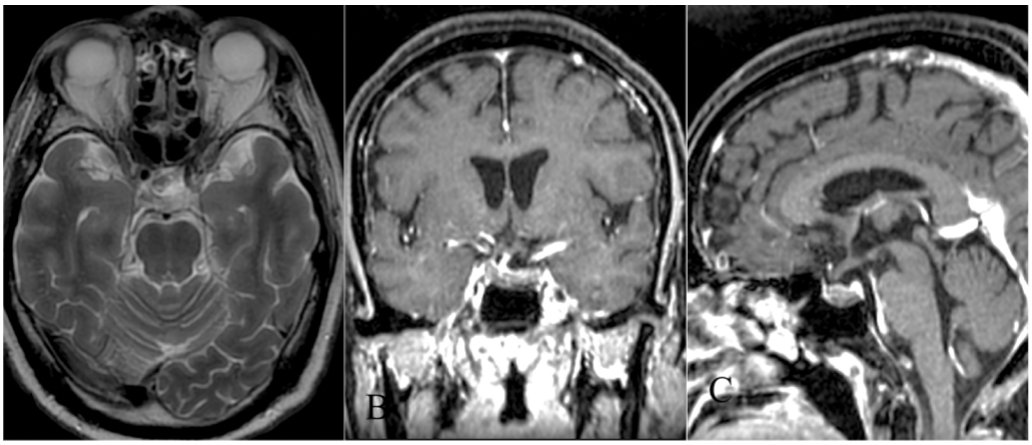


Figure 2. Repeat T2-weighted (A) and contrast-enhanced T1-weighted (B, C) cranial MRI performed 4 months after the first one showed marked regression in the size of the sellar- suprasellar tumor, now measuring 0.4 x 0.2 x 0.2 cm.



("Spontaneous regression" or "spontaneous remission" or "disappearance")]. Handsearching of additional studies was also done by going through the reference section of relevant studies and reviews.

Relevant articles were identified by two authors who independently searched the above databases using the search strategies developed. After deduplication, the titles and abstracts of the remaining studies were assessed. Full-text articles meeting the screening criteria were then retrieved and evaluated using predetermined eligibility criteria. When disagreements arose, these were resolved with the contribution of the third author and by consensus. Studies that satisfied the eligibility criteria were included in the final qualitative analysis.

Data collection and analysis

We extracted data from the included studies using standardized tables that detailed the following information: title, citation, setting, design, total population, and patient demographics.

Neurologic, endocrinologic, and radiologic outcomes were obtained where possible. Mean, median, and percentages were used to summarize data.

Results

Included studies

We identified a total of 396 studies from the electronic database search. After deduplication, 191 articles remained. We excluded 156 studies after assessing titles and abstracts. In the end, 23 articles describing 27 patients were included in the qualitative analysis (Figure 3).

Population and clinical presentation

Including our case, a total of 28 patients were included in the review.[4–26] The mean age was 44 years, with a range of 9-74 years. Fifteen patients were male (54%) and thirteen were female (46%). Of the 28 cases, 17 (61%) were NFPA, and 11 were functioning pituitary adenomas (5 were growth hormone-secreting adenomas; 3, Cushing's disease; 2, prolactinomas; and 1, a mixed somatolactotroph adenoma).

Several patients had medical co-morbidities and possible risk factors. Seven patients (25%) had hypertension and five (18%) had diabetes mellitus, and half of these patients had functioning growth hormone-secreting adenomas or Cushing's disease that are associated with these conditions. Two patients had a recent history of emergency surgery; one patient underwent coronary artery bypass graft and the other had a cholecystectomy. Two patients had a history of mild traumatic brain injury. One patient had concomitant bacterial meningitis, and one had a history of deep vein thrombosis and on chronic heparin use.

Headache was the most common symptom during the initial presentation, with as many as 79% of patients experiencing this. This was followed by vomiting, blurring of

Figure 3. PRISMA diagram of the search strategy

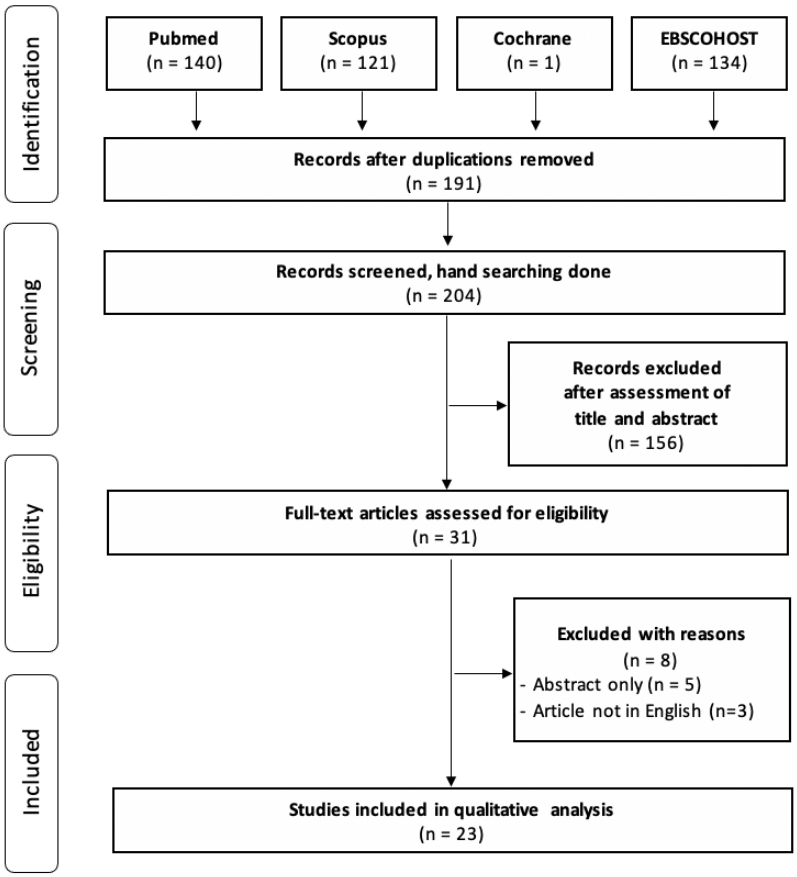


Table 1. Demographic data and outcomes of the patients with pituitary tumors that exhibited spontaneous regression

	Author, Year	Country	Age/ Sex	Diagnosis	Co-morbidity/ risk factor	Radiographic evidence of apoplexy	Radiologic outcome (tumor regression)	Neurologic outcome (symptom resolution)	Endocrinologic outcome (pituitary function)	Follow-up (mos)	Adenoma recurrence
1	Armstrong 1991	USA	66/M	Prolactinoma	Cardiac surgery, HPN	Yes	Complete	Complete	NR	11	No
2	Maccagan 1995	Brazil	42/F	NFPA	None	Presumed (empty sella)	Complete	Complete	Remained PHP	12	No
			51/M	NFPA	HPN Renal failure	Yes	Partial	Complete	Remained HP (thyroid, gonadal)	5	No
			53/F	NFPA	None	Presumed (empty sella)	Complete	Complete	Remained normal	1	No
3	Schatz 2000	USA	57/M	NFPA	None	Yes	Complete	Complete	Remained PHP; SIADH resolved	3	No
4	Kachhara 2000	India	42/M	NFPA	None	Yes	Complete	Complete	Remained normal	12	No
5	Yoshino 2004	Japan	32/M	NFPA (incidental)	Head trauma	Yes	Partial	N/A; asymptomatic	Remained normal	75	No
			35/M	NFPA	None	Yes	Complete	Complete	Remained normal	9	No
6	Wu 2007	China	50/F	NFPA	Decrease in endogenous estrogen	Yes	Complete	N/A; asymptomatic	Central hypogonadism	36	No
7	Alarifi 2005	Saudi Arabia	20/F	Cushing's disease	None	No	Partial	Complete	Central hypogonadism	30	Yes; progression at 24 mos
8	Fraser 2009	Canada	34/M	Acromegaly	Diabetes, HPN	Yes	Partial	Complete	HP resolved	18	No
9	Bahar 2011	Iran	46/F	NFPA	Abnormal liver enzymes	Yes	Complete	Complete	HP resolved	32	No
10	Liu 2012	China	66/M	NFPA	None	Yes	Complete	Complete	HP resolved	3	No
11	Chentil 2012	Algeria	9/M	Somato-lactotroph	None	Yes	Partial	Complete	NR	2	No
12	Machado 2013	Brazil	36/F	Cushing's disease	Diabetes, HPN	Presumed (tumor regression)	Complete	Complete	Remained normal	34	No
13	Villar-Taibo 2013	Spain	51/F	Acromegaly	Bacterial meningitis	No	Complete	Complete	Remained PHP, with diabetes insipidus	1.5	No
14	Jackson 2015	USA	29/F	Prolactinoma	None	Yes	Partial	N/A; asymptomatic	NR	1.8	
15	Zielinski 2015	Poland	59/F	NFPA	DVT on heparin	Yes	Complete	Complete	Remained PHP	60	No
16	Roerink 2015	Netherlands	41/M	Acromegaly	Diabetes	Presumed (tumor regression)	Complete	Partial	NR	24	No
			47/F	Cushing's disease	Diabetes, HPN, obesity	Yes	Partial	Complete	NR	12	Yes; progression at 36 mos
17	Kameno 2016	Japan	13/F	NFPA	Head trauma	No	Complete	Complete	Remained normal	24	No
18	Eichberg 2018	USA	46/F	NFPA	None	Yes	Complete	Complete	Remained normal	48	Yes; recurrence at 42 mos
19	Bilos 2019	Croatia	74/M	NFPA	Abdominal surgery, HPN	Yes	Partial	Partial	HP resolved	9	No
20	Sans-Separa 2019	Spain	50/M	Acromegaly	None	No	Partial	Complete	Remained PHP	6	No
21	Raeesa 2020	India	22//F	NFPA	None	Yes	Complete	Complete	HP resolved	0.5	No
22	Alam 2021	India	40/M	Acromegaly	None	Presumed (tumor regression)	Complete	Partial	Remained normal	NR	No
23	Komic 2021	Croatia	54/M	NFPA	None	Yes	Complete	Complete	HP resolved	6	No
24	Sedano 2022	Philippines	66/M	NFPA	Diabetes HPN	Yes	Partial	Complete	Remained HP (thyroid, gonadal)	12	No

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vision, diplopia, and retro-orbital pain. One patient was asymptomatic, and the tumor was incidentally discovered after cranial imaging for mild head injury. (Table 2)

On neurologic examination, five patients (18%) had decrease in visual acuity and 3 (11%) had visual field cuts. Cranial neuropathies in the oculomotor (18%), trochlear (7%), and abducens nerves (7%) were also reported.

Imaging findings

Hemorrhage in the sellar-suprasellar area, suggestive of pituitary apoplexy, was reported in 68% of cases. Five cases (18%) were presumed to have undergone apoplexy due to findings of an empty sella or complete tumor regression on repeat cranial imaging. The remaining four cases (14%) were speculated to be due to pituitary infarction or spontaneous necrosis.

Only 26 cases provided imaging that was available for review. The MRI and CT images showed acute and subacute hemorrhage in 17 cases (65%). Ten of the 26 images showed T1 and T2 hyperintensity in the center of the tumor, denoting subacute blood. Meanwhile, peripheral tumor enhancement and sphenoid mucosal enhancement were seen in 9 (35%) cases that did not exhibit tumor hemorrhage. (Table 3).

Outcomes

The outcomes were subdivided into neurologic, radiologic, and endocrinologic. The follow-up ranged from 0.5 to 75 months, with a mean of 18 months.

Neurologic outcome

Majority of patients reported resolution of symptoms after regression of the pituitary adenoma, except for two. One patient with growth hormone-secreting adenoma had persistent dysgnathia, while another patient with NFPA had persistent oculomotor nerve palsy. However, many studies did not report the patient's symptoms or neurologic examination findings in detail post-remission.

Table 2. Signs and symptoms of patients with pituitary tumors that exhibited spontaneous regression

Presenting symptoms	**Number (%)**
Headache	22 (79%)
Vomiting	6 (21%)
Blurring of vision	6 (21%)
Diplopia	2 (7%)
Retro-orbital pain	2 (7%)
None	1 (4%)
Neurologic deficits	
Decreased visual acuity	5 (18%)
Visual field cuts	3 (11%)
CN III palsy	5 (18%)
CN IV palsy	2 (7%)
CN VI palsy	2 (7%)

Table 3. Summary of the radiographic findings of the cases of pituitary tumors that exhibited spontaneous

Finding	**Number***
Evidence of hemorrhage	
Yes	17
No	9
Peripheral tumor enhancement	
Yes	10
No	16
Sphenoid enhancement	
Yes	7
No	14
Timing of first repeat cranial imaging	
< 1 month	4
3 months	13
3-6 months	5
6-12 months	3
> 12 months	1
Timing of second repeat cranial imaging	
< 1 month	0
3 months	1
3-6 months	1
6-12 months	4
> 12 months	9
No repeat imaging	13
Radiologic outcome	
Complete resolution/ empty sella	17
Stable residual	8
Recurrence	3

**Based on cases that had imaging available for review*

Radiologic outcome

Complete resolution of the tumor was the most common finding, seen in 18 cases (64%), 13 of which were NFPAs and 5 were functioning adenomas. Ten tumors (36%) only decreased in size; 4 of them were NFPAs and 6 were functioning adenomas.

Half of the authors repeated the cranial imaging 3 months after the spontaneous regression of pituitary adenomas. The earliest documented complete resolution was 17 days, and the longest was 6 years. The earliest documented progression or recurrence was 2 years from the initial imaging.

Tumor recurrence occurred in 3 cases (12%). Two of these were patients with Cushing's
disease wherein the tumor progressed from previously stable residual disease. In terms of the timeline, the Cushing's disease cases recurred after 2-3 years, whereas the lone NFPA recurred after 4 years. Two of the patients with tumor recurrence underwent surgical resection, while one underwent radiation therapy.

Endocrinologic outcome

Prior to spontaneous regression of the pituitary adenomas, 11 patients (40%) had panhypopituitarism in the adrenal, thyroid, and gonadal axes. One of these patients also had persistent diabetes insipidus. Three (11%) had thyroid and gonadal axis deficiencies and 3 (11%) had pure central hypogonadism. One patient had SIADH that was corrected prior to spontaneous regression.

After spontaneous regression was documented, repeat hormonal work-up showed that only 5 patients (22%) continued to have panhypopituitarism. Two (9%) patients each had thyroid and gonadal hypopituitarism and central gonadal hypopituitarism, respectively.

Based on these findings, the recovery rate for hypopituitarism was 40%. However, this figure may not be accurate since only 23 of the 28 studies reported hormonal levels on follow-up.

DISCUSSION

According to our review, majority of patients with spontaneous regression of pituitary adenomas had NFPAs. Most patients exhibited neurologic and endocrinologic improvement concomitant with the regression or resolution of the tumor.

Proposed theories

Spontaneous regression of pituitary adenomas is most often attributed to pituitary apoplexy, a clinical syndrome characterized by headache, visual deficits, altered sensorium, and endocrine dysfunction.[28,29] These symptoms and signs are associated with the abrupt pathological changes of infarction, hemorrhage, or a mixed picture of hemorrhage and infarction within a pituitary tumor.[30] In fact, some authors argue that the hemorrhagic and infarctive types of apoplexy are the same entity on different parts of the spectrum or timeline.[23,30] Pituitary apoplexy is usually considered a neurosurgical emergency, but several studies have shown that it may be more common and less morbid than previously thought.[31–33] Ischemic necrosis and hemorrhage into the necrotic pituitary tumor have both been isolated on histology, despite the lack of clinical symptoms.[30] It has also been found that the incidence of asymptomatic hemorrhage in pituitary adenomas is as high as 68%.[6] Given these findings, it is reasonable to think that pituitary apoplexy may also have a benign clinical course.

Multiple theories have been proposed for the pathogenesis of apoplexy, but the exact mechanism is unknown. Armstrong et al. surmised that compression of feeding vessels or tumor growth beyond the capability of their vascular supply predisposes to infarction that may or may not be followed by hemorrhage.[4] The infundibular and superior hypophyseal vessels may be compressed against the diaphragma sellae by the growing tumor, resulting in ischemia andinfarction.[18]

Microthrombi in infarctive apoplexy may also cause direct vascular occlusion, leading to tumor necrosis.[34] Unlike the normal pituitary gland, the blood supply to pituitary adenomas is reduced; moreover, these tumors have limited angiogenesis and reduced vessel density.[34] These factors may contribute to apoplexy.

Risk factors for apoplexy include cardiac surgery,[4] anti-coagulant treatment,[18] head trauma,[8] hypo- and hypertension,[35] infection,[16] diabetes mellitus/diabetic ketoacidosis,[8] and decrease in circulating

endogenous estrogen. Diabetes may have a detrimental effect on the microvasculature of the pituitary gland, whereas estrogen decrease leads to hyperstimulation of the gland. [23,36]

Another theory is the reduced blood flow within the pituitary gland secondary to the initial hemorrhage, which may have caused a transient increase in intracranial and intrasellar pressure. The initial ischemia may be followed by a phase of hyperemia. [18]

Some authors postulated that meningitis may result in the deposition of necrotic material in the suprasellar subarachnoid space, leading to vasculitis and thrombosis.[16] One of the cases in the review had bacterial meningitis prior to the regression of the pituitary adenoma.

Imaging findings and endocrinologic sequelae

Magnetic resonance imaging (MRI) is the gold standard in the imaging of pituitary adenomas, with a sensitivity of 91% in diagnosing pituitary apoplexy. 13 It can also differentiate the two forms of apoplexy: hemorrhagic and infarctive. Unlike hemorrhagic apoplexy, there is no intrasellar hemorrhage on MRI in pituitary infarction. Other MRI findings include low signal intensity on T1 and T2, and absent or peripheral enhancement of the tumor.[30,37] Enhancement of the sphenoid sinus mucosa may also be seen in pituitary infarction; this may be due to venous congestion caused by the sudden increase in intrasellar pressure, leading to thickening of the mucosa and enhancement on contrast. [18]

In terms of hormonal outcomes, infarctive apoplexy is more liable to involve the tumor itself and spare the gland; thus, it is associated with decreased rates of hypopituitarism compared with the hemorrhagic type. Pituitary insufficiency usually develops after hemorrhagic apoplexy, whereas pituitary function is more commonly preserved after infarctive apoplexy.[18,38]

Learning points

Many learning points were garnered from this review. The first is that pituitary apoplexy may have a clinically benign or silent course, and that it may lead to spontaneous regression of the pituitary adenoma.[4,5,39] Several authors have proposed a conservative approach with close supervision for patients with normal or mild and stable neuro-ophthalmolgical signs and symptoms. [39,40]

The second is the cranial imaging findings and timing of repeat imaging. Neurosurgeons are more familiar with the imaging findings of hemorrhagic apoplexy, but the infarctive type has distinctive features such as enhancement of the sphenoid sinus mucosa, which suggests that the tumor could undergo spontaneous regression. As for the timing of repeat imaging, our review showed that 50% of the tumors already exhibited regression at the three-month scan, so this timeline can be used as a guide when requesting for imaging. Subsequent imaging studies may be performed after 1-2 years since the reported recurrences were detected at least two years after the initial imaging. This would have significant implications in a developing country such as ours, where patients have to pay out-of-pocket for imaging studies.

Lastly, pituitary adenomas may recur after spontaneous regression. This highlights the need to continue regular neuro-ophthalmologic and radiologic follow-up, and patients should be advised about the risk of recurrence.

CONCLUSION

Spontaneous regression of pituitary adenomas is a rare occurrence that is thought to be due to pituitary apoplexy. Most patients exhibited neurologic and endocrinologic improvement concomitant with the regression of the tumor. However, these tumors may recur; thus, regular and long-term neuro-ophthalmologic and radiologic follow-up is advised.

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Appendix A. Search strategy used in identifying articles from major scientific databases

Table 1. Search terms and items found in MEDLINE by Pubmed

	Search Terms	Items Found
1	“Pituitary mass” or “pituitary tumor” or “pituitary adenoma” or “pituitary neoplasm” or "Pituitary Neoplasms"[Mesh]	34,188
2	MRI or “magnetic resonance imaging” or neuroimaging or “Magnetic Resonance Imaging”[Mesh]	853,809
3	“Spontaneous regression” or “spontaneous remission” or “disappearance” or “Neoplasm Regression, Spontaneous”[Mesh]	74,433
4	#1 and #2 and #3	140

Table 2. Search terms and items found in Scopus

	Search Terms	Items Found
1	“Pituitary mass” or “pituitary tumor” or “pituitary adenoma” or “pituitary neoplasm”	36,659
2	MRI or “magnetic resonance imaging” or neuroimaging	1,100,794
3	“Spontaneous regression” or “spontaneous remission” or “disappearance”	114,045
4	#1 and #2 and #3	121

Table 3. Search terms and items found in Cochrane

	Search Terms	Items Found
1	“Pituitary mass” or “pituitary tumor” or “pituitary adenoma” or “pituitary neoplasm”	440
2	MRI or “magnetic resonance imaging” or neuroimaging	42,225
3	“Spontaneous regression” or “spontaneous remission” or “disappearance”	3,387
4	#1 and #2 and #3	1

Table 4. Search terms and items found in EBSCOHOST

	Search Terms	Items Found
1	“Pituitary mass” or “pituitary tumor” or “pituitary adenoma” or “pituitary neoplasm”	41,734
2	MRI or “magnetic resonance imaging” or neuroimaging	1,554,654
3	“Spontaneous regression” or “spontaneous remission” or “disappearance”	164,168
4	#1 and #2 and #3	176

Table 5. Search terms and items found in ClinicalTrials.gov

Search Terms	Items Found
(“Pituitary mass” or “pituitary tumor” or “pituitary adenoma” or “pituitary neoplasm”) AND (MRI or “magnetic resonance imaging” or neuroimaging) AND (“Spontaneous regression” or “spontaneous remission” or “disappearance”)	0