# Pituitary Apoplexy Complicating Chronic Secondary Amenorrhea

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Three young women who developed amenorrhea secondary to large, unsuspected pituitary tumors are described. They presented with acute onset of the triad of headache, nausea and vomiting, and visual abnormalities. One patient died; the other two retained some sequelae, and one had a significant hemiparesis. These devastating effects of pituitary apoplexy can be avoided in amenorrheic patients if the possibility of a pituitary tumor is considered early on. Lateral skull x-ray examinations are inexpensive and easily obtained and will usually demonstrate significant pituitary tumors. Early recognition and surgical removal of pituitary tumors carries low morbidity and mortality and will avoid an apoplectic crisis.

Tumors of the pituitary gland account for approximately 8 to 9 percent of all primary intracranial tumors.[1] Although they are rarely malignant, their manifestations may be devastating either from local mass effect or disturbance of hormonal function.[2] Both hormonal hypersecretory and absence syndromes of all the specific pituitary hormones are well described.[3] In autopsy studies, between 4.6 and 10 percent of patients with pituitary tumors have areas of hemorrhagic necrosis.[4,5] Wakai et al recently noted that in over 9 percent of 560 patients with documented pituitary tumors, the initial presentation was a major or minor hemorrhage into the tumor.[6] However, the initial primary diagnosis of pituitary apoplexy is rare, though it is usually dramatic and may be life threatening.[4-22] Early recognition and aggressive medical and surgical management are therefore mandatory.

Three patients with secondary amenorrhea who developed pituitary apoplexy are reported to focus attention on this syndrome and to describe specific recommendations for clinical management.

## Case Reports

### *Case 1*

A 21-year-old woman developed a severe, throbbing bifrontal headache followed two hours later by nausea and vomiting. She remained awake and alert but suffered severe photophobia. She had been amenorrheic for two years after previously having had normal menstrual periods. She was also being followed by an ophthalmologist because of decreased visual acuity in the right eye, but visual field testing had not been performed. A gynecologist had placed her on an estrogen-progesterone regimen that had partially relieved

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Figure 1. Lateral skull x-ray film demonstrating an enlarged, eroded sella turcica (Case 1)

her amenorrhea, but no further evaluation was undertaken. She specifically denied heat intolerance, recurrent infections, previous severe headaches, or recent weight changes. Her general physical and neurologic examinations were considered normal six hours after the onset of symptoms, except for a macular scar in the right optic fundus. There was no nuchal rigidity or abnormality of secondary sex characteristics or distribution of body hair.

Within 24 hours after admission the patient was lethargic, although easily aroused; both pupils were nonreactive to light, and she developed mild nuchal rigidity. A lumbar puncture revealed pink, turbid spinal fluid with a supine opening pressure of 210 mm. The red blood cell count was 9,200/mm$^3$ and the white blood cell count was 7,200/mm$^3$ with 94 percent polymorphonuclear leukocytes. The protein was 174 mg/100 mL, and the glucose was 91 mg/100 mL. Over the next 24 hours she became confused, disoriented, and unable to follow commands consistently. Her vision deteriorated to total bilateral blindness. High doses of corticosteroids were started, and within eight hours she was awake, alert, and oriented. She still had no light perception in the right eye and there was a dense temporal field loss in the left. The acuity of the left eye was 20/20. Skull x-ray films revealed a markedly enlarged, eroded sella turcica (Figure 1). A computed tomographic (CT) brain scan revealed an intrasellar mass lesion (Figure 2). Bilateral carotid and vertebral angiography failed to demonstrate any displacement of vessels, tumor stain, or aneurysm.

A transseptal transsphenoidal hypophysectomy was performed on the second hospital day. After opening the dura, liquid necrotic sellar contents were removed by aspiration. The walls of the sella were inspected, but no solid tissue was identified. During the immediate postoperative period the patient was awake, alert, oriented, and without paresis, but she had no significant change in her vision. Four hours after surgery she suddenly developed a left hemiparesis and became disoriented and confused; there was no light perception in either eye, and both pupils were nonreactive to light. A repeat CT scan did not demonstrate tumor or hemorrhage. Bilateral carotid angiography showed marked spasm of the supraclinoid portion of the right internal carotid artery.

Eight hours later she was lucid and oriented once again. The left hemiparesis persisted. Light perception was present in both eyes and she was able to count fingers with the right eye. Ten days after surgery her visual acuity was 20/400 in the right eye and 20/80 in the left, with persistent bitemporal hemianopia. Both pupils reacted to light.

Over the next year her vision did not change significantly. She learned to walk with a short leg brace. Her left arm remained partially paralyzed, but her facial movements were normal. She did not require endocrine replacement therapy. A repeat CT scan showed no recurrent tumor. There has been no return of menses. She returned to school able to care for herself independently despite her partial hemiparesis.

### *Case 2*

A 36-year-old woman awakened abruptly at 3:30 AM with a vertex headache. Over the next five

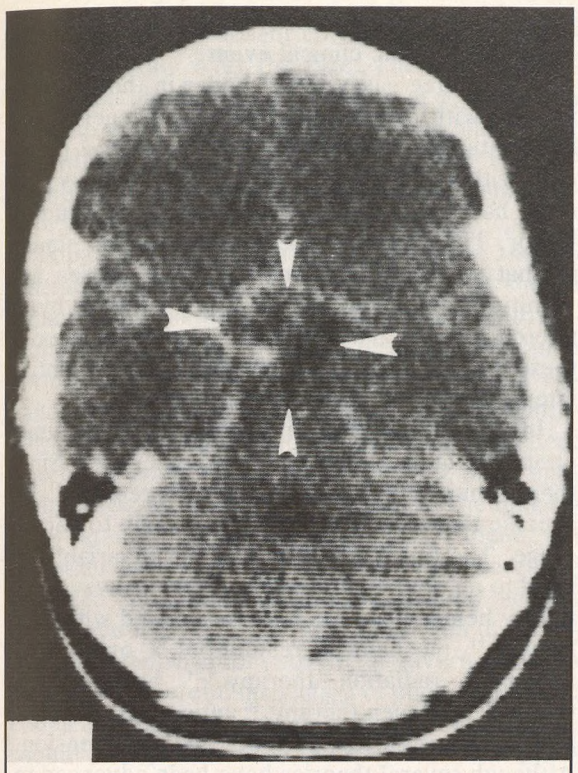

Figure 2. CT scan of the sella revealing mass lesion in an enlarged sella turcica (Case 1)

days the headache remained constant and moderately painful but was not associated with nausea, vomiting, or visual disturbance. There were no other associated complaints. She had had irregular menstrual periods from menarche at age 14 years until the onset of amenorrhea at age 22 years. She had decreased libido and had been previously noted to have an infantile uterus.

Physical examination by the family physician revealed a pulse of 56 beats per minute, blood pressure 100/70 mmHg, and temperature of 98°F. Her general and neurologic examinations were normal except for tenderness over the frontal and maxillary sinuses and mild pharyngitis. Her optic fundi, visual fields, and extraocular movements were described as normal. There was no stiff neck and no motor or sensory abnormality. Two days later the patient became nauseated and began vomiting. She was admitted to the hospital that evening and had a major seizure. The patient lost consciousness, her pupils became fixed and dilated, and she died three hours after admission.

Massive hemorrhage into a pituitary chromophobe adenoma, which involved the hypothalamus and third ventricle, were demonstrated at necropsy. The sella was enlarged to approximately 2.5 times normal, and the brain was diffusely and markedly edematous, weighing 1,350 g. Other findings included atrophic adrenal glands, atrophy of the internal and external genitalia, and a small follicular adenoma of the thyroid.

### *Case 3*

A 29-year-old woman was admitted to the hospital 36 hours after the acute onset of sudden, severe headache behind the left eye and in the left temporal region. The headache was associated with nausea and vomiting, which subsided after 12 hours. She also complained of marked diplopia in all directions of gaze. Pertinent past history included amenorrhea and loss of libido since the birth of her last child four years previously.

Physical examination revealed a pulse of 80 beats per minute, blood pressure 100/70 mmHg, and temperature of 100°F. The patient was apathetic but cooperative. There was no nuchal rigidity or other signs of meningismus. Both pupils reacted to light, although the left was slightly sluggish, and there was anisocoria, with the left pupil measuring 4 mm and the right 3 mm. She had complete loss of abduction of the left eye and weakness of all other eye muscles, including minimal ptosis on the left. No corneal reflex could be elicited on the left. The tendon reflexes were all hyperactive but equal bilaterally. There was Hoffmann's sign on the left and an equivocal left Babinski response. The remainder of the examination was within normal limits. Fundi showed no evidence of papilledema, and there were no visual field abnormalities detected on confrontation testing. A lumbar puncture revealed clear colorless fluid under normal pressure. The blood cell count was within normal limits, and there was no elevation of protein.

It was thought at first that the patient might have a cavernous sinus thrombosis, and for this reason x-ray films were made of the paranasal si-

nuses. These films demonstrated enlargement and duplication of the floor of the sella as well as parasellar calcification. The dorsum sellae, posterior clinoids, and left anterior clinoid process were demineralized. After six days of steroid administration the left ptosis had improved, the other extraocular movements were unchanged, the headache had diminished, and the visual acuity was 20/40.

The patient was thought to have a pituitary chromophobe adenoma with lateral extension from the sella toward the left. The sudden onset of headache and diplopia suggested hemorrhage into the tumor. X-ray therapy was started on the seventh hospital day with an initial dose of 50 rads, increasing daily by 200-rad increments to a total dose of 4,000 rads. When the patient was seen by an ophthalmologist on the 12th hospital day, it was noted that there was bitemporal hemianopia to red and bilateral superior temporal quadrantanopia to white on the right. This had not been noted on the initial hospital examination. The patient was discharged on the 16th hospital day to continue x-ray therapy as an outpatient.

The headache disappeared completely, and complete function returned to the third, fourth, fifth, and sixth cranial nerves. Nine months following the acute illness, she indicated that her menses had begun one month after cessation of the x-ray therapy and had remained regular for four months until she became pregnant. At the time of that visit she was three months pregnant. There was a persistent right superior quadrantanopia, but the field defect had disappeared from the left eye. The last report of the ophthalmologist, six years after the initial illness, stated her visual acuity was 20/20 in each eye and her visual fields were normal.

## Discussion

Tumors of the pituitary gland must be suspected in any patient with amenorrhea. It is not often emphasized, however, that patients with a pituitary tumor may have sudden, unexpected, life-threatening hemorrhage into the tumor. Each of the patients presented could have been diagnosed and treated before the apoplexy occurred, thus avoiding a catastrophic clinical event.

These three cases were similar in that all were women with secondary amenorrhea, each had a large pituitary tumor, each was seen by a physician within two years prior to the apoplexy, but none had been examined for a possible pituitary tumor. The clinical presentation was also similar in that each had sudden headache, nausea and vomiting, and visual abnormalities followed by an altered state of consciousness. Also, in all three of these cases the diagnosis was not apparent until a lateral skull x-ray film was examined.

In 1905, Bleibtrau first recognized pituitary apoplexy in a patient with acromegaly.[8] Since then, a number of cases have been reported. No specific tumor type appears more likely to hemorrhage. The onset is abrupt and not invariably related to an obvious triggering event. However, pituitary hemorrhage has been associated with head trauma,[11] mechanical respirators,[12] open heart surgery,[15] radiation therapy,[5,21] bromocriptine therapy,[6] estrogen therapy,[16] anticoagulation therapy,[18] the postpartum period,[19] and hypertension.[9] Although several theories have been advanced regarding precipitating causes for the hemorrhage, the underlying etiology remains unclear.

The most common presenting symptoms are sudden severe headache, loss of vision, nausea and vomiting, and ocular disorders.[6] The headache probably results from stretching of the intrasellar and diaphragmatic dura or from meningeal irritation. Periorbital and frontal headache are the most common, though the headache may occur anywhere. Nausea and vomiting may be related to meningeal irritation, hypothalamic dysfunction, or increased intracranial pressure. Hypothalamic involvement is also indicated when hyperpyrexia is present. Common visual symptoms are diplopia, photophobia, and blurred vision. Ocular signs include extraocular muscle palsies, pupillary changes, and visual field defects. Papilledema or optic atrophy secondary to chronic increased intracranial pressure may be present. The typical visual field defect is bitemporal hemianopia, indicating chiasmal involvement from extrasellar extension of the tumor. The visual field defects are variable, however. Tumor extension laterally into the cavernous sinus is the usual cause for extraocular muscle palsies and trigeminal nerve involvement, which, although uncommon, manifests

as a decreased or absent corneal reflex or diminished sensation over the face. The state of consciousness almost always is altered at some time in the course of pituitary apoplexy. Nuchal rigidity and other signs of meningeal irritation are frequently observed and are secondary to subarachnoid hemorrhage.

In patients with secondary amenorrhea, the initial radiographic evaluation is critical and should include plain skull films and a computed tomographic brain scan on a high-resolution machine both with and without intravenous contrast enhancement. If either of these tests suggests a pituitary tumor, cerebral angiography is indicated. Thorough endocrinologic, neurologic, and ophthalmologic evaluation is mandatory. The diagnosis of pituitary tumor is ordinarily not difficult. On the other hand, pituitary apoplexy may be easily confused with meningitis, subarachnoid hemorrhage secondary to a ruptured aneurysm or arteriovenous malformation, stroke, or cavernous sinus thrombosis. Careful inspection of plain skull films, coupled with an appropriate clinical evaluation, should strongly increase the suspicion that pituitary apoplexy has occurred.

Pituitary apoplexy is such a life-threatening event that once the diagnosis is made, treatment should be instituted immediately. The patient with x-ray evidence of an enlarged or eroded sella turcica, a history of sudden headache and visual abnormalities, and an altered state of consciousness should be started promptly on high doses of corticosteroids. This is administered both as replacement therapy and to decrease the attendant brain swelling and meningeal reaction that usually accompanies the bleeding. When progressive visual disturbance or an increase in intracranial pressure has occurred, as evidenced by an altered state of consciousness, surgical intervention is the treatment of choice. The transseptal transsphenoidal microsurgical technique allows for rapid, thorough removal of the pituitary neoplasm and accompanying hematoma and should be performed as an emergency procedure.[14] Mortality from this procedure in elective cases of pituitary tumor is less than 1 percent, but it is higher in emergency situations such as in pituitary apoplexy.[23] This increased risk serves only to emphasize the need to diagnose the tumor before it hemorrhages. Following surgery, specific hormone replacement therapy should be given as indicated by endocrinologic evaluation. Radiation as an alternative therapy for nonoperated patients should be individualized, since in some cases there is evidence that the apoplexy itself has destroyed the tumor, making further therapy for the tumor itself unnecessary.

## References


1. Butler AB, Netsky MG: Classification and biology of brain tumors. In Youmans JR (ed): Neurological Surgery. Philadelphia, WB Saunders, 1973, vol 3, pp 1292-1339
2. Jenkins JS: Pituitary Tumors. London, Butterworths, 1973
3. Sotos JF: Pituitary Tumors. In Gardner LI (ed): Endocrine and Genetic Diseases of Childhood. Philadelphia, WB Saunders, 1969, pp 120-199
4. Lopez JA: Pituitary apoplexy. J Oslo City Hosp 20:17, 1970
5. Wersberg LA: Clinical study of pituitary apoplexy with emphasis on five cases precipitated by radiotherapy. Neurology 26:353, 1976
6. Wakai S, Fukushima T, Teramoto A, Sano K: Pituitary apoplexy: Its incidence and clinical significance. J Neurosurg 55:187, 1981
7. Benjamin JE: Pituitary tumor with fulminating symptoms. JAMA 92:1755, 1929
8. Bliebtrau L: Ein fall von acromegalia (Zerstorung der hypophysis durch bluntunt). MMW 52:2079, 1905
9. Broughan M, Heusner AP, Adams RD: Acute degenerative changes in adenomas of the pituitary body with special reference to pituitary apoplexy. J Neurosurg 7:421, 1950
10. Conomy JP, Ferguson JH, Brodkey JS, et al: Spontaneous infarction in pituitary tumors: Neurologic and therapeutic aspects. Neurology 25:580, 1975
11. Daniel PM, Spicer EJF, Treip CS: Pituitary necrosis in patients maintained on mechanical respirators. J Pathol 111:135, 1973
12. Dawson BH, Kothandaram P: Acute massive infarction of pituitary adenomas. A study of five patients. J Neurosurg 37:275, 1972
13. Fountain EM, Baird WC, Poppen JL: Pituitary apoplexy: A report of three cases with recovery. Lahey Clin Bull 7:117, 1951
14. Kosary IZ, Braham J, Tadmor R, Goldhammer Y: Transsphenoidal surgical approach in pituitary apoplexy. Neurochirurgie 19:234, 1976
15. Kovacs K, Yao J: Pituitary necrosis following major heart surgery. Z Kardio 64:52, 1975
16. Locke S, Tyler HR: Pituitary apoplexy: Report of two cases, with pathological verification. Am J Med 30:643, 1961
17. Post MJD, David NJ, Glaser JS, et al: Pituitary apoplexy: Diagnosis by computed tomography. Radiology 134:665, 1980
18. Rovet RL, Fein JM: Pituitary apoplexy: A review and reappraisal. J Neurosurg 37:280, 1972
19. Sheehan HL: Postpartum necrosis of the anterior pituitary. J Pathol 45:189, 1937
20. Shenkin HA: Relief of amblyopia in pituitary apoplexy by prompt surgical intervention. JAMA 159:1622, 1955
21. Wersberg LA: Pituitary apoplexy: Association of degenerative change in pituitary adenoma with radiotherapy and detection by cerebral computed tomography. Am J Med 63:109, 1977
22. Zervas NT, Mendelson G: Treatment of acute haemorrhage of pituitary tumors. Lancet 1:604, 1975
23. Wilson CB, Denipsey LC: Transsphenoidal microsurgery removal of 250 pituitary adenomas. J Neurosurg 48:13, 1978