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CASE REPORT

PATHOLOGY/BIOLOGY

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Sudden and Unexpected Death from Pituitary Tumor Apoplexy

ABSTRACT: Pituitary tumor apoplexy refers to a clinical syndrome precipitated by the expansion of a pituitary adenoma by hemorrhage or infarction. Individuals may present with myriad signs, including sudden onset of severe headache, visual changes, altered mental status, cranial nerve palsies, and hormonal dysfunction. This disorder constitutes a medical emergency and warrants an expedited evaluation, diagnosis, and treatment to prevent the potential sequelae of permanent visual loss, endocrine abnormalities, or death. We report a case of sudden death from undiagnosed pituitary tumor apoplexy. The decedent was evaluated by medical personnel on three occasions in the week prior to her death for severe headache, nausea, vomiting, and photophobia. Postmortem examination demonstrated a hemorrhagic infarction of a pituitary adenoma with necrosis and expansion out of the sella turcica. The recognition of and treatment for a patient with pituitary tumor apoplexy requires a rapid multidisciplinary effort. Failure of prompt diagnosis may be fatal and require a medico-legal death investigation for sudden and unexpected death.

KEYWORDS: forensic science, forensic pathology, pituitary adenoma, tumor, apoplexy, sudden death

Pituitary tumor apoplexy (or pituitary apoplexy) refers to a clinical syndrome involving a constellation of signs and symptoms that are a result of expansion of the sella turcica (1). The large majority of cases involve hemorrhage or infarction of a preexistent pituitary adenoma; thus, the term "pituitary tumor apoplexy" is commonly utilized to describe this condition. Rare cases of hemorrhagic infarction of a normal pituitary gland during pregnancy, known as Sheehan's syndrome, involve pronounced postpartum bleeding associated with hypotension (1). A case of hemorrhage into the pituitary was initially published in 1898 by Bailey (2). In 1950, Brougham et al. (3) coined the term "pituitary apoplexy" and summarized the symptomatology and pathological findings of five individuals who died suddenly and whose postmortem examinations revealed hemorrhage and necrosis of a pituitary adenoma.

The clinical presentation of pituitary tumor apoplexy generally includes the following: a severe and abrupt headache in up to 100% of affected patients, deterioration in visual acuity leading to blindness, visual field defects (bitemporal hemianopsia), and ophthalmoplegia (usually involving the cranial nerves III, IV, and VI) as well as nausea, vomiting, lethargy, meningismus, and altered level of consciousness (1,4–7). In addition, the majority of patients have decreased levels of pituitary hormones, or panhypopituitarism, resulting from increased intrasellar pressure, destruction of the gland, or deficits because of adenoma (6,7). The condition has been reported in individuals ranging between 6 and 90 years with a mean age of 50.9 years (1,7,8). Pituitary adenomas constitute *c.* 10% of intracranial tumors, and the reported incidence of apoplexy ranges from 0.6 to 27% (4,7). There is a higher male-to-female ratio, reported as 2:1 (1,7,8).

Sudden death following pituitary tumor apoplexy is rarely reported in the medical literature and, in particular, in specialty journals or texts serving the forensic community. The present case report discusses the clinical, pathological, and legal implications arising from pituitary tumor apoplexy. In addition, we highlight the prototypical presentation, differential diagnoses, diagnostic studies, and treatment inherent in this life-threatening condition.

Case History

A 46-year-old woman experienced sudden collapse at home. Upon arrival of the emergency medical squad, she was unresponsive, diaphoretic, and asystolic. She underwent cardiopulmonary resuscitation and was admitted to the Emergency Department (ED). Resuscitation efforts were unsuccessful, and she was pronounced dead. The coroner initially suspected that the cause of death was a myocardial infarction.

The decedent had visited health care organizations on three occasions during the week prior to her death, complaining of headaches associated with nausea and vomiting of several days' duration. At her first ED visit 7 days before death, she was diagnosed with hypertension and volume depletion. One week earlier, she had experienced edema of the lower extremities bilaterally. Use of a prescribed diuretic led to resolution of these symptoms. She denied headaches, blurred vision, or dizziness. Three days after the ED visit, she was evaluated by her family physician for the recently diagnosed hypertension and was prescribed an alternate antihypertensive medication.

The decedent presented to the ED 1 day prior to death with a 3-day history of a "throbbing diffuse headache," which was recorded by the ED physician as "the worst headache they [sic] have ever had." She had a history of migraine headaches; however,

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the headache on that day was more intense and was associated with nausea, vomiting, and photophobia. She denied neck stiffness, blurred vision, fever, phonophobia, or a history of trauma related to her symptoms. Seizure activity was not reported. The physical examination demonstrated reactive pupils with conjugate gaze and without deviation to either side or nystagmus. Fundoscopy was negative for papilledema, hemorrhage, or exudate.

A cephalic CT scan revealed evidence of a mass in the sella turcica measuring at least 1.6 × 3.0 cm, which was coupled with complete opacification of the sphenoid sinuses bilaterally, an air-fluid level, and mucosal thickening (Fig. 1). The cerebral ventricles were normal without midline shift or mass effect. In addition to the diagnosis of sphenoid and ethmoid sinusitis, the differential diagnosis of the sellar mass included a pituitary neoplasm. The victim was discharged home as the "current examination was not consistent with acute subarachnoid hemorrhage, meningitis, or other conditions requiring immediate intervention" per the ED physician's report.

The decedent had a history of polypharmacy, including treatment for hypertension and hypothyroidism. Her surgical history was significant for a remote total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Autopsy Findings

The decedent was a normally developed, obese woman appearing several years older than the reported age of 46 years. She measured 5 feet 6 inches and weighed 227 pounds (body mass index = 36 kg/m^2). The external examination of the body did not reveal any significant findings. The internal examination was limited to cranial and cardiac examination specifically with inspection *in situ* of all organs and major structures in the cervical, thoracoabdominal, and pelvic cavities. The brain weighed 1220 g with a mild degree of brain swelling characterized by slight constriction of the structures in the region of the basilar cisterns. The pituitary fossa exhibited a soft tan/red tumor with focal hemorrhage anteriorly in the region of the optic nerves (Fig. 2). The tumor was expansive, protruded slightly out of the sella turcica superiorly, and measured up to 1.9 cm transversely by up to 1.3 cm in the anterior–posterior direction. The mass weighed 4.5 g and was prominently enlarged, markedly soft, necrotic, and focally hemorrhagic with a mottled pale tan/red and gray/green discoloration and interdigitating regions of maroon/blue clot. The enlarged pituitary fossa had a probed depth of 1.5 in (3.18 cm) (Fig. 3). The bone at the base of the fossa was soft and allowed a small probe to extend through it with mild pressure. Loss of bone mass was attributed to remodeling and thinning of the wall. The bulging pituitary neoplasm pressed against the optic nerve at the optic chiasm and was slightly adherent to the nerve sheath. It also caressed the undersurface of the mamillary bodies. The tumor protruded upward but did not erode into the paper-thin bone on the sides of the fossa.

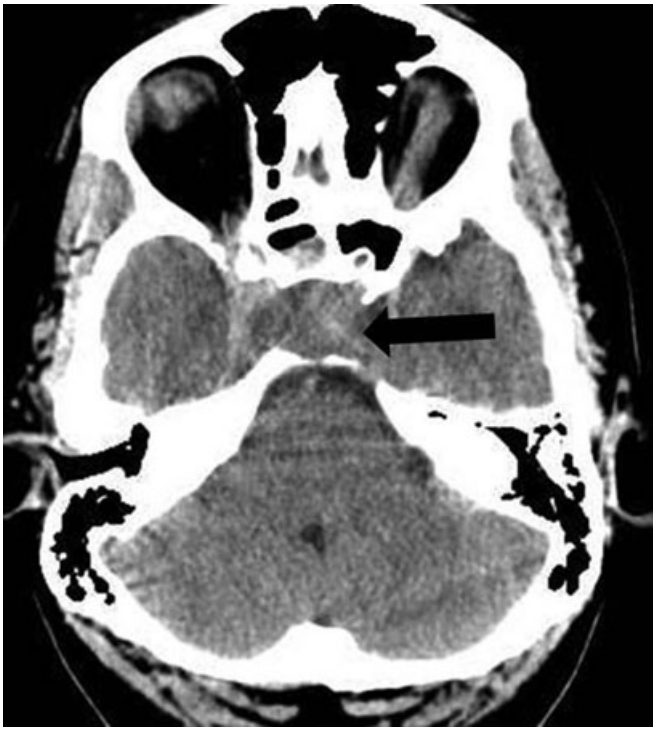

FIG. 1—*Axial image of the head CT revealing the mass in the sella measuring 1.6 × 3.0 cm.*

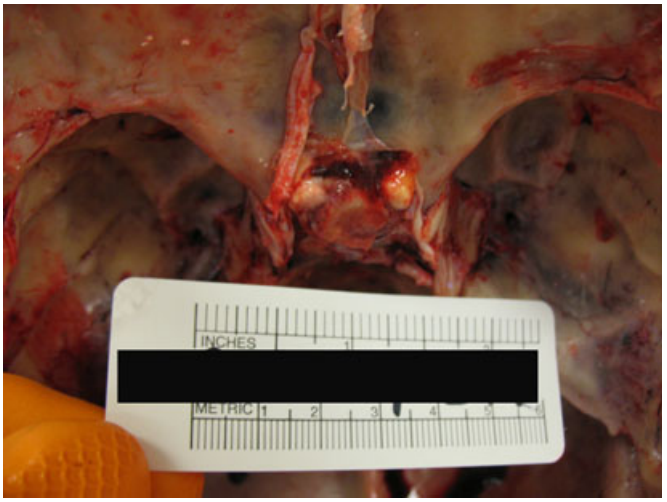

FIG. 2—*Expansive hemorrhagic tumor in the pituitary fossa that compresses the optic nerves.*

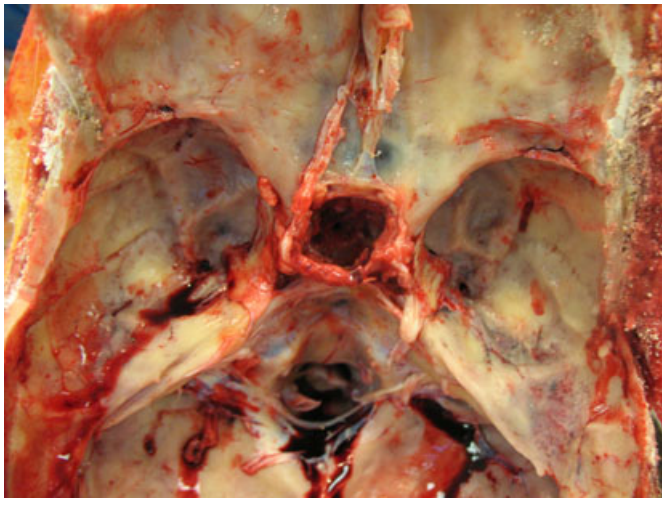

FIG. 3—*Following resection of the pituitary tumor, the pituitary fossa is significantly enlarged because of the size of the tumor.*

In addition to the pituitary tumor, other findings of note consisted of pulmonary edema and hyperemia, chronic lymphocytic thyroiditis, and hepatomegaly with a moderate degree of large droplet fatty change.

Postmortem Toxicology

A peripheral blood screen was positive for caffeine. A urine screen detected the following opiates: hydrocodone, 281 ng/mL; hydromorphone, 704 ng/mL; oxycodone, 110 ng/mL; and the metabolite, oxymorphone, 81 ng/mL.

Histological Studies

Histological investigation of multiple sections of the pituitary mass by routine hematoxylin–eosin-stained slides disclosed the presence of an adenoma, which was composed of small, uniform polygonal cells oriented in sheets and cords (Fig. 4). The cytoplasm of the adenoma cells was uniformly eosinophilic. The adenoma focally was acutely infarcted with an array of hypereosinophilic "ghost cells" and scattered infiltrates of polymorphonuclear leukocytes.

Discussion

The management of pituitary apoplexy has improved over the decades, primarily because of four factors: (i) enhanced diagnostic accuracy; (ii) use of glucocorticoids; (iii) progressively improved supportive therapy; and (iv) advancements in surgical techniques and postoperative care (1). Despite a greater sophistication in treating patients with pituitary apoplexy, the risk of morbidity and mortality without treatment is high. Studies published prior to the use of corticosteroid treatment for this condition indicated a mortality rate of *c.* 50% (3).

Forensic pathologists infrequently encounter intracranial neoplasms presenting as sudden and unexpected death. The incidence of undiagnosed fatal brain tumors, which were initially detected at autopsy, has ranged between 0.02 and 0.4% (9–11). Eberhart et al. (10) suggest that improved imaging studies over the past 20 years have led to early detection of cranial neoplasms, in turn decreasing the number of undiagnosed brain tumors.

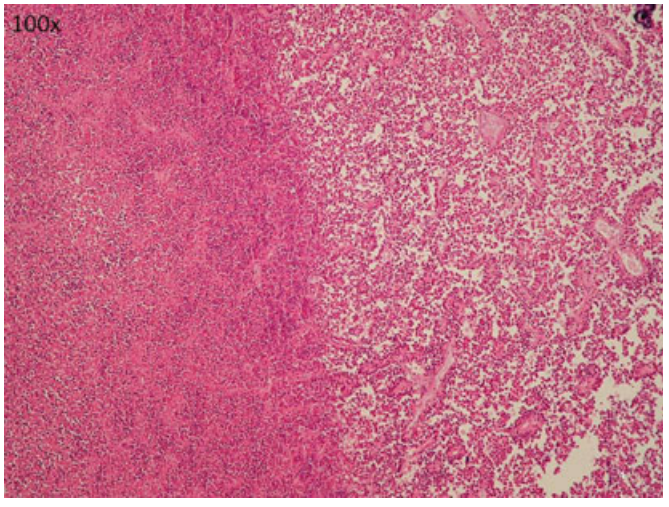

FIG. 4—*Histological view of the pituitary tumor composed of small, uniform polygonal cells disposed in sheets and cords that were focally acutely infarcted with hypereosinophilic "ghost cells" and early infiltrates of neutrophils (100×).*

Pituitary tumor apoplexy has seldom been addressed in the forensic literature. Bauer et al. (12) described a 41-year-old man who had presented 6 months prior to his death with headaches and blurred vision. Imaging studies were not performed at the time; however, on physical examination, visual field and visual acuity were not affected, and a neurological examination including an electroencephalogram was normal. He was diagnosed with cervical tension syndrome and treated with a cervical collar and cervical anesthetic injections. His symptoms did not resolve, and he died suddenly and unexpectedly, which prompted a medico-legal examination. The forensic autopsy revealed a 4.0×3.0 cm encapsulated pituitary mass with extension to the skull base and compression of the optic chiasm and hypothalamic region. Histological analysis demonstrated acute hemorrhage within the tumor. Pursuant to German civil law, a malpractice lawsuit was filed based on the allegation of neglect by failure to perform timely radiological testing 6 months prior to the victim's death at the initial presentation; the charge was subsequently dismissed.

The legal implications inherent in pituitary tumor apoplexy have spawned considerable attention. David, reporting on six cases of pituitary tumor apoplexy, highlights each case history with commentary on the medical and legal aspects (13). The underlying message focuses on the common thread of delayed diagnosis, mismanagement of patients suffering from an apoplectic episode, and misdiagnosis of this condition, all of which culminated in either permanent physical impairment or death. David stressed that this syndrome is not widely appreciated by most physicians in primary care clinics and in the ED (13).

The patient in the present study was evaluated by several physicians in the week prior to her death, specifically, two ED visits and one appointment with her family physician. Her initial complaint in the ED was a history of edema of the lower extremities bilaterally, and she was diagnosed with hypertension and volume depletion. Antidiuretic hormone is produced in the hypothalamus and stored in the posterior pituitary. A pathological process involving the posterior pituitary—we postulate—may have caused neurogenic diabetes insipidus, resulting in volume depletion. Abnormalities of posterior pituitary function are rare in individuals with pituitary tumor apoplexy; however, partial, transient diabetes insipidus results in *c.* 10% of patients in the immediate postoperative period for this condition (1).

Despite the autopsy findings in this case of focal hemorrhage in the anterior pituitary fossa in the region of the optic nerves and expansion of the pituitary tumor with pressure against and adherence to the optic chiasm, the patient did not complain of any visual symptoms except for photophobia. She did not have evidence of visual field or cranial nerve abnormalities by physical examination in the ED on the night before her death.

On the evening prior to her death, the victim in this report underwent a cranial CT scan in the ED, which revealed a sellar mass and prompted the differential diagnosis of a pituitary neoplasm. The radiologist had not released his report of his impression of the CT scan until after the patient was discharged. In the wake of this critical communication failure, we speculate that the ED physician, who evaluated the patient, most likely failed to recognize the cranial abnormality on the scan. Consequently, he reported the CT scan as "negative," and he did not consult either a neuroradiologist or neurosurgeon prior to discharging the patient home. In his differential diagnosis, he had considered subarachnoid hemorrhage and meningitis but had not considered the correct diagnosis. Our case demonstrates numerous similarities to David's study (13), which focuses on the legal repercussions related to pituitary tumor apoplexy. Several physicians, namely a primary care physician and

ED physicians, came into contact with the deceased on numerous occasions in the week prior to her death. In each encounter, the condition was not a component of the recorded differential diagnosis, which led to erroneous treatment. Even after the CT scan was performed, the abnormality of the pituitary fossa was not recognized by the treating physician.

It has been reported that up to 25% of pathological studies involving surgically resected or pituitary adenomas first diagnosed at autopsy may exhibit spontaneous hemorrhage, even in the absence of any overt, premonitory symptoms (1,7). Between 50 and 90% of patients spontaneously experienced pituitary apoplexy without a previous diagnosis of a pituitary adenoma (1,5–8). Contrarily, incidental pituitary adenomas discovered at autopsy may have no correlative antemortem symptomatology. Auer et al. (14) reported three cases of incidental macroadenomas at autopsy of tumor diameters measuring between 2.5 (two cases) cm and 4.0 cm without hemorrhage or necrosis. The ready availability of brain MRI scans has facilitated an increase in detection of asymptomatic pituitary adenomas, known as "pituitary incidentalomas" (15).

The prompt recognition of pituitary apoplexy in the clinical setting is a challenge owing to its similarities with several other life-threatening conditions. Primary among these are ruptured intracranial aneurysm resulting in subarachnoid hemorrhage, bacterial or viral meningitis, myocardial infarction, cerebrovascular hemorrhage (stroke), shock, midbrain infarction, cavernous sinus thrombosis, and migraine headache (1,5,7,16). Both pituitary apoplexy and subarchnoid hemorrhage share the symptoms of sudden, severe headache, impaired consciousness, photophobia, and stiff neck (1,7). In addition, symptoms of pituitary apoplexy and bacterial meningitis have considerable overlap, namely altered mental status, fever, headaches, lethargy, and meningismus (1,7,17–19). The omnipresent symptom of severe headache, namely "thunderclap headache" in patients presenting with pituitary apoplexy, creates an even greater degree of difficulty in the differential diagnoses (20–22). Because of the high risk of morbidity and mortality in most of these conditions, radiological imaging is urgently required.

The decedent in the present study presented to the ED 1 day prior to death with a 3-day history of a "throbbing diffuse headache," which was reported by the ED physician as "the worst headache they [sic] have ever had." Although she had a history of migraine headaches, the headache on that day was more intense and was associated with nausea, vomiting, and photophobia. The ED physician opined these symptoms were related to subarachnoid hemorrhage and meningitis as he discharged the patient after these urgent conditions were ruled out.

In cases of suspected pituitary apoplexy, either a CT scan or MRI is urgently necessary to verify a sellar mass or hemorrhage. The MRI is preferred to the CT scan as the former provides a more detailed view of the cranial anatomy, including the optic involvement, suprasellar and cavernous sinus extension, and carotid artery visualization to rule out the presence of an aneurysm (1,5–7).

The confirmed diagnosis of pituitary apoplexy warrants a multidisciplinary action composed of neurosurgeons, ophthalmologists, and endocrinologists. Immediate administration of high-dose corticosteroids is mandatory to restore hemodynamic stability as these patients may have experienced acute adrenal insufficiency because of compression or destruction of a normal pituitary gland (6,16). In cases when an individual has symptoms of visual impairment including sudden onset of blindness, hypothalamic abnormalities, or diminished level of consciousness, a transsphenoidal surgical decompression performed by a skilled neurosurgeon is warranted (5).

Conclusion

The accurate diagnosis of pituitary tumor apoplexy may prove challenging owing to the similarity of symptoms with numerous other emergent, complex conditions, most notably, subarachnoid hemorrhage resulting from aneurysm rupture and bacterial and viral meningitis. The misdiagnosis and/or delayed diagnosis of this life-threatening condition may lead to permanent visual abnormalities or death. Heightened awareness of this syndrome is mandatory in both the primary care and ED settings. Prompt recognition of pituitary tumor apoplexy confirmed by indicated CT and/or MRI scans facilitates a multidisciplinary investigation, including involvement by endocrinologists, ophthalmologists, and neurosurgeons. Such specialists, respectively, provide hemodynamic stabilization, confirm the extent of visual abnormalities, and perform transsphenoidal decompression. Failure to recognize and appropriately treat pituitary tumor apoplexy in a clinical setting may result in a victim's sudden and unexpected death necessitating a forensic investigation. The forensic pathologist should not only be capable of diagnosing the heterogeneous pathological findings of an infarction, hemorrhagic infarction, or hemorrhage of a pituitary adenoma but also thoroughly review the clinical history associated with pituitary tumor apoplexy to accurately ascribe the proximate cause of death.

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