VASCULAR LESIONS IN PITUITARY ADENOMAS*

C. F. LIST, M.D.; J. R. WILLIAMS, M.D., and G. W. BALYEAT, M.D.

Grand Rapids, Michigan

(Received for publication September 21, 1951)

The textbook picture of a disease is developed by isolating schematically its salient features from a large variety of clinicopathologic observations and by attempting to reduce them to a common denominator. This endeavor of systematization certainly gratifies the urge of logical thinking, but by its arbitrary simplification tends to construct a fixed pattern which is only reluctantly discarded if new and perhaps contradictory facts are discovered.

A good example of such a situation is found in our state of knowledge concerning hypophyseal adenoma. The well-known textbook concept of this type of neoplasm dates back to Cushing's classical description. With growing experience, however, confusing and therefore neglected variants of the disease had to be reconsidered. Jefferson, for instance, gave an excellent analysis of unusual pituitary adenomas with extrasellar extension.

In this article we propose to depict another aspect of the kaleidoscopic pituitary syndrome, viz., the vascular lesions occurring in pituitary adenoma. Knowledge of this condition is by no means new, and sporadic reports may be found even in the older literature. Brougham, Heusner, and Adams1 deserve credit for having collected all these reports; and on the basis of 5 new observations have redirected our attention to the problem. Since their publication we were able to find 3 additional articles dealing with this subject.4,6,7

The paucity of references in the literature may have created the impression that vascular lesions in pituitary tumors are very rare; but the discussion following the delivery of our paper at the Harvey Cushing Society meeting in April 1951 convinced us that similar cases are not exceptional at all, and that they pose challenging diagnostic and therapeutic problems. Whereas Brougham, Heusner, and Adams' paper dealt with 5 clinicopathologic observations verified by autopsy, we wish to present in full 3 clinical cases with favorable outcome. The first case was seen by one of us at the University of Michigan Hospital.‡ The other two observations were made in private practice.


History. The patient had been in good health except for amenorrhea which followed appendectomy 15 years ago. Two weeks prior to admission, she complained

† 29 Sheldon Avenue, Grand Rapids 2, Michigan.
‡ We wish to express our appreciation to Dr. E. A. Kahn who kindly permitted us to publish this case.
of severe right supraorbital headache and difficulty in elevating the right upper eyelid. Within a few days, vision of the right eye gradually declined, finally progressing to total blindness. She became confused, restless, and, on the day before admission, lapsed into a semicomatose state.

Examination. The patient was semicomatose, disoriented, incoherent, and resistive. Temperature 105.6°F; pulse 130; respiration 16. B.P. 90/70. Her skin was of unusually fine texture, white and dry. Pubic and axillary hair were absent. There was marked nuchal rigidity and Kernig’s sign was positive bilaterally. Both pupils were fixed to light, the right one being dilated. There was also a right-sided ptosis of the upper lid and divergent strabismus indicative of a 3rd nerve palsy. The patient did not respond to light stimuli. The fundi showed slight blurring of the nasal disk margins. She moved all her extremities spontaneously and equally. The plantar responses were extensor, and a right-sided Rossolimo sign was present. The abdominal reflexes were absent.

The clinical impression was that of spontaneous subarachnoid hemorrhage, probably from ruptured basal aneurysm on the right.

Fig. 1. (A) Case 1. Enlarged sella. (B) Case 2. Arteriogram. Note slightly erect and opened carotid siphon. (C) Case 3. Intrasellar erosion. (D) Case 3. Recalcification and reduction in size of the sella following x-ray therapy.
Lumbar puncture yielded a brick-red fluid under pressure of 280 mm. The fluid was loaded with fresh and crenated red blood cells. Total protein was 266 mg. per cent; gold curve 1122100000; mastic 334332; Kahn negative. Urine contained albumin and granular casts. RBC 5.79 million; Hb. 93 per cent. WBC 28,300: 88 per cent polymorphs, 10 per cent lymphocytes, 2 per cent mononuclears. Roentgenograms of the skull demonstrated a marked degree of intrasellar erosion suggesting the presence of a pituitary adenoma (Fig. 1A).

**Course.** Within a week’s time the patient’s general condition improved. Fever, confusion, and meningeal signs subsided and the blood disappeared from her spinal fluid, but the ocular findings, viz., the right 3rd nerve palsy and blindness, remained unchanged. After she had recovered sufficiently, carotid angiography was done (on the 24th hospital day) in order to differentiate between bleeding aneurysm and pituitary tumor. This procedure showed no anomaly of the vascular tree of the carotid, and therefore the presumptive diagnosis was made of chromophobe pituitary adenoma with hemorrhage spilling into the subarachnoid space.

**Operation.** On her 26th hospital day a right frontal craniotomy disclosed xanthochromic and hemorrhagic discoloration of the orbital surface of the right frontal lobe. The chiasm and optic nerves were displaced by a bluish-black hemorrhagic tumor mass which, on aspiration, yielded no blood. After incision of the capsule, a hemorrhagically infarcted pituitary adenoma was thoroughly removed.

**Histologic Examination.** There were scattered foci of well preserved chromophobe pituitary adenoma with large areas of complete ischemic infarction, old and fresh hemorrhages, hemosiderin deposits, and areas of infiltration with polymorphonuclear leukocytes and macrophages (Figs. 2 and 3).

**Postoperative course** was uneventful, but the patient remained completely blind when discharged on her 40th hospital day. When last heard of, 6 years later, she was still blind and without sense of smell. She had no other subjective complaints and was working as a Dictaphone operator.


**History.** This patient had been in good health except for intermittent, bilateral frontotemporal headaches of 10 years’ duration. Thirty-six hours prior to admission, a violent bifrontal headache suddenly developed, associated with nausea and vomiting. A few hours later, marked loss of vision occurred in both eyes, particularly in the left, and the left upper eyelid began to droop. The patient’s daughter observed that her mother became mildly confused, showed some difficulties in expressing herself, and displayed impairment of memory and lack of concern towards her illness. By the time of admission, headaches and nausea had somewhat abated, but the ocular signs persisted. The patient’s menstrual periods had become irregular at age 46, occurring at 3- to 6-month intervals.

**Examination.** The patient was moderately obese but showed no other constitutional change. She was slightly drowsy, with slowed cerebration, indifferent mood, and impaired memory and judgment. A slight degree of nominal aphasia was present. Temperature was elevated to 103°, but all other vital signs were normal. There was mild rigidity of the neck. The left eye was practically blind, and there was loss of temporal field on the right. Both optic disks showed a mild degree of primary optic atrophy. Complete paralysis of the left 3rd nerve was noted, as well as mild
Fig. 2. Case 1. Photomicrographs of operative specimen. (A) Pituitary adenoma with sclerotic thick-walled arteriole. Fresh hemorrhage above. (B) Hemorrhage and necrosis with beginning organization above. Adenomatous tissue below.

Paresis of the left 4th and 6th nerves. The right upper extremity showed slightly reduced strength with diminished deep reflexes.

A presumptive diagnosis of left carotid aneurysm with subarachnoid hemorrhage was made.

X-rays of the skull showed typical intrasellar type of erosion with barely visible, erect posterior clinoid processes. Since this finding suggested the presence of a pitui-
VASCULAR LESIONS IN PITUITARY ADENOMAS

When an adenoma, the previously planned lumbar puncture was omitted and further laboratory data were obtained. Blood sugar was 109 mg. per cent; glucose tolerance test showed a diabetic curve with elevation to 257 mg. per cent in the first hour and 1+ sugar in the urine. Cholesterol was 207 mg. per cent; B.M.R. was +39.

Course. Within a few days, the meningeal signs subsided and some vision returned in the left temporal field. In consideration of a diagnosis of an aneurysm, left carotid arteriography was performed on the 4th hospital day (Fig. 1 B). This demonstrated no aneurysm, but the parasellar portion of the carotid artery appeared to be a trifle elevated, the siphon stretched, and the terminal supraclinoid portion narrowed with delay of the outflow of contrast medium. The angiogram was compatible with a diagnosis of a pituitary adenoma, yet it was felt necessary to determine by ventriculography more accurately whether or not there was a supra- or parasellar extension of the tumor. Ventriculograms were normal, ruling out sizable extrasellar extension.

Operation. Because of persistent visual loss and ocular palsies and in the absence of significant signs of hypopituitarism, a left frontal craniotomy was undertaken on the 14th hospital day. A tumor mass was seen to extend underneath the left optic nerve and tract. Old hemorrhage had stained the surface of the left optic nerve. During removal of the tumor an unusual avascular grayish-white appearance of part of the tissue was noted.

Histologic Examination. The specimen proved to be a chromophobe adenoma with marked secondary changes indicative of infarction. There were areas of necrosis, and other areas of old and fresh hemorrhage. The cells of the adenoma had undergone considerable degenerative changes, and in certain places there was marked infiltration with inflammatory cells and young fibroblasts.

Fig. 3. Case 1. Photomicrograph of operative specimen (high magnification). Pituitary adenoma with macrophages containing hemosiderin granules.
Postoperative course was uneventful except for transient euphoric indifference and confusion, but on discharge (31st hospital day) the mental changes had practically disappeared. There was residual right homonymous hemianopsia. The paralysis of the 3rd nerve had started to improve and the function of the 4th and 6th nerves was normal. B.P., and fluid intake and output were normal. Subsequent laboratory studies 6 months later showed B.M.R. —30, glucose tolerance test normal, cholesterol 142 mg. per cent, urinary 17-ketosteroids 13.2 mg. per cent, serum potassium 20.4 mg. per cent, and normal eosinophil response to adrenaline and A.C.T.H. Since hypophysal function was considered adequate, deep x-ray therapy was given, totaling a tumor dose of 1620 r. When last seen, she was mentally normal and without complaints. Incomplete right homonymous hemianopsia and very slight paresis of the left 3rd nerve were still demonstrable.


History. Twenty-four hours prior to admission, the patient suddenly had violent bilateral frontoparietal headaches associated with nausea and vomiting and a feeling of exhaustion. He had had, for the past 15 years, occasional attacks of right-sided headaches which were diagnosed as migraine. His past record revealed no other significant factors except for a history of a subtotal thyroidectomy in 1944.

Examination. The patient was a moderately obese man with a pale, pasty skin. He was slightly drowsy and confused, and had occasional difficulty in expressing himself. Temperature was elevated to 102–103°, but other vital signs were normal. Moderate nuchal rigidity was noted. Eyegrounds and gross visual fields were normal.

A tentative diagnosis of spontaneous subarachnoid hemorrhage was made. On spinal tap, the fluid was pinkish and under pressure of 240 mm.; it contained 1025 crenated RBC; 48 WBC; total protein was 101.7 mg. per cent; sugar 49.5 mg. per cent.

Roentgenograms of the skull revealed a considerable degree of intrasellar erosion with elongated thinned posterior clinoids and ballooned floor of the sella* (Fig. 1 C). This unexpected finding posed new diagnostic problems: Did this patient have a bleeding basilar aneurism which had eroded the sella, did he have a hemorrhage into an unsuspected pituitary adenoma, or was this perhaps a combination of both conditions?

Course. His rather unusual course helped to clarify the situation. After the signs of meningeal irritation had subsided, carotid angiography was planned, but a new dramatic development forced us to forego this procedure. On the 11th hospital day, after a sustained gradual improvement, the patient went into profound shock. His color became ashen, his systolic blood pressure dropped to 60, there was nausea, weakness and drowsiness, and his blood sugar level, which was previously found to be 148 mg. per cent, sank to 58 mg. per cent. Plasma chlorides were 400 mg. per cent. This syndrome suggested acute adrenal insufficiency (Addisonian crisis). Immediate specific therapy (adrenal cortex extract, intravenous glucose in saline) was instituted, followed by prompt improvement. However, milder relapses occurred, each responding to the same therapy.

During all this time the patient exhibited extreme lassitude, was confused and

---

* Of interest were skull x-rays, later made available, dated 1935 and 1944. The former showed a normal sella, the latter early ballooning.
drowsy, and had occasional paranoid delusions. Furthermore, he complained of blurred vision and diplopia. Repeated neurologic examination disclosed merely a mild paresis of the left inferior rectus but no changes in his vision or visual fields. It was evident that his precarious state precluded drastic diagnostic or surgical measures. The profound systemic reaction was interpreted as acute hypopituitarism produced by hemorrhage and infarction into an almost asymptomatic pituitary adenoma, leading to the secondary symptoms of adrenal insufficiency. The more recent ocular signs were thought to indicate possible pressure of the expanded adenoma on neighboring structures. In order to prevent progression of eye signs, roentgen-ray therapy of the pituitary gland was reluctantly started. On the day of the second x-ray treatment the patient again became desperately ill with peripheral vascular collapse, nausea, and vomiting; but again he responded to adrenal cortex therapy, glucose and saline, which was continued throughout his hospital stay. Further cautious irradiation was well tolerated, until, after 28 days, a total tumor dose of 1446 r was reached. The patient improved slowly and diplopia, visual blurring, and mental changes disappeared, and he was discharged.

The patient was maintained with daily intramuscular desoxycorticosterone acetate in a dose of 3.5 mg., supplemented with methyl testosterone 20 mg., thyroid extract 130 mg., ascorbic acid 200 mg., and a high salt, high protein, high carbohydrate diet with interval and bedtime feedings. He became fully active and returned to work on this regime but further increase in well-being was noted when cortisone orally in a daily dose of 20 mg. replaced the desoxycorticosterone acetate.

Detailed laboratory data relative to his endocrine status have been obtained on several occasions over the past 3½ years. The Kepler water test was positive in both water excretion and chemical portion with total calculated figure of 20 obtained. Urinary 17-ketosteroids were found to be only 2.5 mg./24 hours on one occasion and 1.9 mg./24 hours on another. Blood cholesterol varied from 224 to 470 mg. per cent. Basal metabolism varied from −25 to −41. Glucose tolerance curve was very low and flat, starting with fasting values of 55 and 60 mg. per cent. A.C.T.H. produced no fall in the circulating eosinophils. Further episodes of acute adrenal insufficiency occurred subsequently, the last one in November 1950 following an acute gastro-intestinal infection. Nevertheless, the patient was maintained in satisfactory endocrine balance on a daily regime of cortisone 20 mg., testosterone and thyroid 0.13 gm. Checkup skull films showed recalcification of the dorsum sellae (Fig. 1D).

CLINICOPATHOLOGIC CONSIDERATIONS

Every neurosurgeon is familiar with the fact that pituitary adenomas are highly vascular tumors which easily become imbibed with blood when traumatized. In postoperative autopsy specimens of large pituitary adenomas, one is often amazed to find the entire tumor mass hemorrhagic, even though the area of surgical interference was very limited. It is not clear what causes a spontaneous vascular accident in a pituitary adenoma but there is reason to believe that the growth rate of neoplastic cells may outstrip their blood supply and that increased intracapsular pressure favors ischemia and thrombosis. Once infarction has occurred, a large portion of the adenoma, or even the entire tumor, becomes a hemorrhagic mass that swells up as rapidly as a soaked sponge. Such sudden increase
of volume and of intracapsular tension produces acute compression of neighboring structures. First of all, the optic nerves, chiasm and optic tract, already impinged by the bulk of the pre-existing adenoma, suffer additional serious damage. Later on, pressure may be exerted extradurally against the structures of the cavernous sinus. If the hemorrhagically infarcted adenoma or actual clot formation extends into the parasellar subarachnoid space, the 3rd nerve is encroached upon intradurally and carotid circulation interfered with. An adjacent pituitary lesion may not only compress the carotid mechanically but may also induce local vasospasm by irritation. Finally, sudden suprasellar expansion of the adenoma may compress the hypothalamic region, jeopardizing its blood supply. It is not surprising that some blood may escape into the basilar subarachnoid space, or that, even in the absence of gross hemorrhage, an infarcted adenoma may set up an inflammatory reaction in the basilar cisterns.

With the knowledge of this pathologic background, the neurologic symptomatology may be better understood. In most cases the syndrome follows a fairly constant train of events. It must be emphasized that the presence of a pituitary adenoma frequently was not even suspected before the acute episode. Most of the patients had surprisingly few and uncharacteristic premonitory symptoms. Perhaps the most striking example is the case described by Dingley.\(^2\) His patient, a man in apparently excellent health, ran after a moving bus, and, after he had boarded, dropped over dead. Autopsy showed as the only abnormal finding, massive hemorrhage in a previously asymptomatic pituitary adenoma. In our own observations the patients merely complained of occasional intermittent headaches but gave no inkling of the presence of an intracranial growth. The onset is always dramatic. The initial signs and symptoms such as violent headache, nausea, vomiting, nuchal rigidity, drowsiness and confusion, and elevation of temperature point to the diagnosis of spontaneous subarachnoid hemorrhage. Indeed, the spinal fluid is usually bloody or may show a mild polymorphonuclear inflammatory reaction. In contrast to the insidious onset of symptoms in the average case of pituitary tumor, signs of local damage to adjacent neural structures develop abruptly. Rapid loss of vision, even total blindness, appears to be characteristic of vascular accident in a pituitary adenoma (Case 1 and Case 2). This is illustrated by the following additional brief observation:

University of Michigan Hospital No. 418703. S.K., male, aged 23. This man experienced, on awakening, sudden loss of vision in the right eye. Several months later there was gradual decrease of vision in the left eye. Operation disclosed a hemorrhagic dark brown cyst in a chromophobe adenoma. Five months postoperatively, the patient again suddenly lost his sight, this time on the left side. When re-operated on, a hemorrhagic cyst was found to have recurred in the residual adenoma.

Acute lesions of the 3rd nerve, less frequently of the 4th and 6th nerves, are likewise common. It must be understood, however, that sudden appear-
ance of these neighborhood signs is not necessarily produced by hemorrhage or infarction, but may merely indicate lateral extension of the tumor (Weinberger, Adler and Grant). Evidence of hemispherical involvement has been reported and was present to some degree in our Case 2. It may be ascribed to an impaired carotid circulation or, in some cases, to direct compression of the hemisphere by clot. Acute damage to the hypothalamus plays at least a contributory role in the development of somnolence, confusion, hyperthermia, and disturbance of vegetative functions; in fact, implication of this vital area adds to the gravity of the clinical course. In the subacute state, the neurologic symptomatology may be complicated by superimposed symptoms and signs of endocrine deficiency (Case 3). A massive vascular accident in the adenoma seriously interferes with hormonal function of the remaining anterior pituitary lobe; thus, acute hypopituitarism ( cachexia hypophyseopriva) results with secondary adrenal insufficiency.

DIAGNOSIS

The acute development of the clinical picture suggests at first the presence of bleeding intracranial aneurysm, but that diagnosis is immediately questioned when roentgenographic evidence of intrasellar erosion is discovered. Cases of this type present a strong argument for early routine roentgenograms of the skull regardless of the patient’s grave condition. The innocuous x-ray examination offers decisive information before potentially dangerous diagnostic steps (such as lumbar puncture, etc.) are carried out. Nevertheless, evaluation of intrasellar erosion in a comatose patient is difficult as the following observation will demonstrate:

Blodgett Memorial Hospital, Grand Rapids, Michigan, No. 50-7143. J.S., male, aged 52.

This man complained of drowsiness and headaches of 2 weeks' duration, and finally became stuporous. There were signs of minimal left hemiparesis. Roentgenograms of the skull showed marked intrasellar erosion and the calcified pineal body was displaced to the left. With such limited information, a tentative diagnosis was made of pituitary tumor with extrasellar extension and/or possible hemorrhage. The patient died before anything more could be done. At autopsy a walnut-sized chromophobe pituitary adenoma without hemorrhage was found, and in addition, a diffuse glioblastoma of the right insular region and adjacent basilar ganglia with marked edema of the white matter of the hemisphere.

When the roentgenograms in the above case were reviewed, the pineal was seen to be shifted not only to the opposite side but also downward, whereas in pituitary tumor with large extrasellar extension one could expect the pineal shift to occur upward.

Admittedly, a large carotid aneurysm may produce an asymmetric intrasellar erosion. Carotid angiography therefore is necessary to exclude aneurysm. The arteriogram may show minor deviation of the course and shape of the carotid artery, at times with evidence of impaired intracranial blood flow. Once the possibility of aneurysm has been eliminated and the
diagnosis of pituitary adenoma rendered probable, two further problems
must be clarified. First, the presence of neighborhood signs always arouses
the suspicion of extrasellar extension. In such a situation, ventriculographic
studies, as recommended by Jefferson\(^5\) and White\(^10\) prove informative, yet
judgment is required as to whether the diagnostic aid gained by ventric-
ulography outweighs the risk of the procedure. The second problem is
to accomplish as thorough an assay of pituitary function as the patient’s
precarious condition permits, utilizing the following tests: BMR, blood
cholesterol, fasting blood sugar and glucose tolerance, Kepler’s water
balance test, fluid intake and output, eosinophil response to adrenalin and
ACTH, and finally urinary 17-ketosteroid determination. These data
furnish an essential base line for further diagnostic and therapeutic manage-
ment and permit early recognition of panhypopituitarism.

**TREATMENT**

Management of the acutely ill patient as illustrated in our observations
should be conservative and supportive until the signs of subarachnoid
hemorrhage have abated. In the meanwhile, laboratory studies will have
determined the patient’s endocrine status. If definite pituitary deficiency
is present, as in our Case 3, surgical diagnostic procedures and operations
are clearly contraindicated. Specific endocrine substitution therapy should
then be given until hormonal decompensation is controlled. Such medication
may have to be continued as a maintenance dose for a long period even
after the acute emergency has passed. It is our present opinion that roentgen-
ray therapy should not be given immediately after a vascular accident has
occurred in a pituitary tumor. In Case 3, for instance, a serious aggravation
of signs and symptoms occurred during irradiation which was administered
assuming a policy of “calculated risk.” This may or may not have been due
to this treatment, nevertheless, there are reports in the literature describing
sudden onset of vascular accidents in pituitary adenoma while roentgen-
ray treatment was under progress (Sosman,\(^8\) Dott, Bailey and Cushing\(^9\)).

In the presence of marked visual loss and paralysis of adjacent cranial
nerves, early surgical intervention is indicated, but it is important to possess
preoperative information concerning possible extrasellar extension of the
tumor. In spite of early evacuation of the infarcted and hemorrhagic
pituitary adenoma, damage to the optic nerves and chiasm may prove
irreversible (Case 1). Postoperative x-ray therapy should be postponed
until endocrine functions have become stabilized.

**SUMMARY**

Pituitary adenomas occasionally tend to undergo vascular changes such as
massive hemorrhage or infarction.

The resulting clinical syndrome is dramatic and puzzling in as much
as the adenoma may have previously produced minimal or no symptoms.
There is acute onset of grave intracranial signs such as subarachnoid or
intracerebral hemorrhage. Blindness or extra-ocular palsies may rapidly develop. Secondary signs of acute panhypopituitarism (with adrenal insufficiency) frequently complicate the picture. The cerebrospinal fluid is either bloody or may show moderate polymorphonuclear pleocytosis. Roentgenograms of the skull disclose typical intrasellar erosion. Carotid angiography may be required to differentiate the condition from bleeding intracranial aneurysm.

If severe loss of vision or extra-ocular palsies have occurred, early operation is indicated, provided there are no signs of acute hypopituitarism. If, however, the clinical syndrome is dominated by evidence of severe panhypopituitarism surgical treatment is inadvisable and even roentgen-ray treatment dangerous; supportive hormonal therapy should then be given.

Three illustrative cases with good outcome are reported.

REFERENCES