Invasive Pituitary Adenomas

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Pituitary adenomas which extend beyond their capsular limits and invade surrounding structures cannot be grouped together into a well-defined clinicopathological unit. They occur infrequently; consequently, the accumulated data concerning their natural history are meager. The problem is confused further by the variability of their gross and microscopic patterns of growth. The following cases are reported in order to extend the collected knowledge of the diverse features of invasive pituitary adenomas.

Material

During the years 1952 to 1963 inclusive, adenoma of the pituitary gland was diagnosed and verified histologically in 53 patients at the Walter Reed General Hospital. Five of the 53 tumors had extended beyond their capsules, involved contiguous structures, and accordingly were considered to be invasive.

Case Reports

Case 1. A 26-year-old Army officer was admitted to the hospital on Sept. 8, 1951, following a 6-week history of left orbital pain, headache and projectile vomiting.

Examination disclosed hemorrhages and papilledema in both ocular fundi, a right homonymous hemianopsia and disorientation. Roentgenograms of the skull showed an enlarged sella turcica consistent with an intrasellar tumor.

Hydrocephalus was diagnosed and attributed to tumor obstructing the 3rd ventricle.

Operation. Following a ventriculocisternal shunt, a left transfrontal craniotomy was accomplished on Sept. 19, 1951. An invasive meaty tumor was found enveloping the optic chiasm, the left optic nerve and tract, with extension into the interpeduncular fossa. Subtotal removal was effected without incident.

Microscopic Examination. The tumor was composed of masses of cells lacking an orderly arrangement. The cytoplasm was agranular, amphiophic, and moderate in amount. The nuclei were pleomorphic and varied from vesicular to pyknotic. Connective-tissue stroma was inconspicuous. Occasional mitotic figures were seen. The blood vessels appeared normal. Mineralization was absent (Fig. 1). Diagnosis of invasive pituitary adenoma with cellular atypism was made.

Course. Following an uneventful recovery, roentgen-ray therapy utilizing the 1000 kv. unit was started on Oct. 3, 1951. Through 7X7 cm. frontal, right and left temporal ports, 4000 r were delivered to the tumor during 45 treatments distributed over 50 days, which were tolerated well.

During the remainder of his hospitalization detailed investigation of his endocrinologic status failed to reveal any abnormality. He was discharged on May 31, 1952. Residual deficit then was limited to the cuts in the visual fields noted on admission, and 20/200 visual acuity of the left eye.

During the ensuing 8 years the patient required replacement therapy with thyroid and cortisone. Despite progressive lethargy and weakness, however, he was able to continue working.

2nd Admission. In September 1960, he became progressively confused and reentered the hospital. Roentgenograms of the skull showed no change from those which were taken in 1951. Left carotid angiogram suggested the possibility of recurrent tumor.

2nd Operation. On Sept. 22, 1960, a right frontotemporal craniotomy was performed and the perisellar region was explored. Recurrent tumor was not found. The leptomeninges were markedly thickened, and the basal cisterns were obliterated.

Course. A ventriculotraial shunt failed to improve his mental status.

He was transferred to another hospital for long-term care because he was unable to look after his own needs. Progressive deterioration of his mental status occurred until death, March 12, 1962. A complete autopsy was performed; the protocol and microscopic sections were available for our study.

Autopsy. Aside from the testicular atrophy, atrophy of the adrenal and thyroid glands, and a mild bronchopneumonia, significant findings were limited to the head. The brain weighed 1850 gm. and showed the residuals of the surgical procedures. The two tubes for shunts had evoked a marked ependymitis. The mammillary bodies,
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Fig. 1. Case 1. Pituitary adenoma. Note pleomorphism. Hematoxylin and eosin, X620.

tuber cinereum and infundibulum were distorted beyond gross recognition. There was a moderate degree of hydrocephalus. The leptomeninges were thickened so that the basal cisterns were obliterated. The sella turcica was greatly enlarged and was empty except for a loose fragment of tissue presumed to be the remnants of the pituitary gland.

The hypothalamus, subthalamus and cerebral peduncles showed sclerotic hyaline vessels and nonspecific gliosis compatible with the effect of radiation. The pia, subpial parenchyma of the basal cisterns, ependyma and subependymal grey of all the ventricles were involved with mililiary noncaseating granulomata. No organisms were seen or cultured. No pituitary tissue, either normal or neoplastic, was identified.

Case 2. A 20-year-old soldier was admitted on Jan. 12, 1954 because of sudden blurring of vision of the left eye 6 weeks previously. His only other symptom was increasingly severe intermittent bifrontal headaches.

Examination revealed a right homonymous hemianopsia with left visual acuity reduced to counting of fingers, and a depressed right corneal reflex. Destruction of the sella turcica and clinoid processes as well as erosion of the left greater and lesser wings of the sphenoid bone were evident on roentgenograms of the skull. Detailed investigation of the function of the endocrine glands disclosed no abnormality.

Operation. A left frontal craniotomy was performed on Feb. 2, 1954. A large tumor was encountered which had destroyed the posterior wall of the orbit on the left and displaced the optic nerve and chiasm superiorly. Extensive involvement of the neighboring structures permitted only attempt at subtotal removal, which was carried out without incident.

Course. He did well for 36 hours and seemed to be making an uneventful recovery, when he became comatose and died 48 hours after operation.

Autopsy. Pertinent findings were limited to the head. The brain weighed 1550 gm. The sella turcica was completely destroyed and replaced by tumor. The optic, oculomotor and trigeminal nerves, bilaterally, were surrounded by the tumor as they emerged from the brain. The tumor extended into the ethmoidal and sphenoidal sinuses and the left orbit. Although displaced and distorted, the brain itself was not invaded by tumor. Extensive recent hemorrhage surrounded the tumor.

Microscopic Examination. The tumor was composed of cells without an orderly arrangement. The cytoplasm was agranular, uniformly eosinophilic and moderate in amount. The nuclei were pale, vesicular and were minimally pleomorphic. Connective-tissue stroma was inconspicuous. Occasional mitotic figures were seen. Blood vessels were normal. There was no mineralization (Figs. 2 and 3). Diagnosis was invasive pituitary adenoma. Death was attributed to postoperative hemorrhage at the operative site.
Case 3. A 39-year-old officer was admitted on May 15, 1953 for evaluation of progressive visual loss for 1 year. Additional questioning disclosed a somewhat longer history of impotency, retro-orbital headaches and increasing weakness.

Examination revealed moderate obesity, bitemporal hemianopsia and pallor of the right optic disc. Visual acuity: OD 20/200, OS 20/70. Roentgenograms of the skull showed destruction of the sella turcica and posterior clinoid processes with bilateral erosion of the greater and lesser wings of the sphenoid bone. Endocrinologic evaluation disclosed minimal hypothyroidism.

Operation. A right frontal craniotomy was performed on May 26, 1953. A tumor, prune-like in color and consistency, was encountered growing from the sella turcica, encompassing the optic chiasm and right optic nerve, and extending onto the right temporal lobe along the lesser wing of the sphenoid bone. The tumor was intimately adherent to the hypothalamic structures and the surface of the temporal lobe. The major portion of the intrasellar mass was removed. The extrasellar extension involving the hypothalamus was left undisturbed. Bleeding from the bed of the tumor was not troublesome.

Microscopic Examination. The tumor showed masses of cells divided into cords and fascicles by blood-filled spaces. The cytoplasm varied in amount and was agranular and amphophilic. The nuclei were pleomorphic with their patterns of chromatin varying from vesicular to clumped. Connective-tissue stroma was inconspicuous. Occasional mitotic figures were seen. Blood vessels were normal. Mineralization was not seen (Fig. 4). Diagnosis of invasive pituitary adenoma with cellular atypism was made.

Course. The patient did well postoperatively. Radiation therapy was begun on June 5, 1953. Utilizing the 1000 kV. unit, 4000 r were delivered to the tumor through 5 x 5 cm. right and left temporal and frontal ports, dividing 92 treatments over 39 days. He tolerated the radiation well.

His condition remained stable during the next 5 months. Visual-field deficits were the same as on admission. A persistent mild weakness of the right lateral rectus muscle occurred after operation. Visual acuity improved to 20/100 OD and 20/50 OS. Replacement therapy with testosterone was started.

2nd Admission. He returned unexpectedly from convalescent leave on Nov. 2, 1953 because of confusion and progressive loss of vision.

2nd Operation. The site of the right frontal craniotomy was reopened on Nov. 6, 1953, and a hematoma was removed from the bed of the tumor. Additional tumor, having the same gross and microscopic appearances as described previously, was removed.

Course. After the 2nd operation, at the time of discharge, the patient's mental status had returned to normal but vision remained severely impaired. He was essentially blind in the left eye. Visual acuity of the right eye was 4/200, with marked constriction of the visual field peripherally, and a temporal hemianopsia.

During the ensuing years, his condition remained stable although he had to take glucocorticosteroid, testosterone and thyroid replacements.

3rd Admission. He was readmitted to the hospital on Feb. 15, 1962 because of increasingly frequent convulsions. Physical findings were unchanged from those noted prior to his discharge. Erosion of the petrous ridge on the right was seen on roentgenogram of the skull. Bilateral carotid angiograms disclosed conspicuous displacement of both carotid siphons and proximal portions of both anterior cerebral arteries.

3rd Operation. A right frontotemporal craniotomy was performed on March 1, 1962. A blue cyst was found beneath the optic chiasm and aspiration of it resulted in the withdrawal of a few cc. of dark red material. Additional tumor was removed from beneath the chiasm. The tumor, which had also invaded the petrous ridge, was composed of a thin shell of viable tissue enclosing a necrotic core.

Microscopic examination of the tumor disclosed no essential difference from the tumor removed in 1953.

![Image](image_url)
Course. Additional radiation therapy was administered, this time with the 2000 kV. unit. Another 4000 r were delivered to the tumor through 6×8 cm. right and left frontotemporal ports, 24 treatments in 31 days being given without complication.

Follow-up investigation in February 1964 disclosed no significant change in his physical status during the previous 2 years. He has been able to engage in part-time work, although severely limited by his visual deficits. Convulsions have not been a problem.

Fig. 3. Case 2. Same tumor as in Fig. 2. Note minimal pleomorphism and occasional mitotic figure. Hematoxylin and eosin, X680.

Fig. 4. Case 3. Pituitary adenoma. Note marked pleomorphism. Hematoxylin and eosin, X620.
Case 4. A 51-year-old recently retired sergeant was admitted on Sept. 8, 1963 because of the sudden onset of severe generalized headaches.

The patient was asymptomatic until approximately 40 hours prior to admission when he experienced the abrupt beginning of generalized increasingly severe headaches. A few hours before admission he noted inability to elevate his right eyelid.

Examination. He was an obese man lying quietly in bed, complaining of headache. Blood pressure was 170/110 mm. Hg. His sensorium was intact. He was able to read print with his left eye. Visual acuity of the right eye was limited to counting of fingers. A complete ophthalmoplegia was present on the right. Extraocular muscles functioned normally on the left. Tactile sensibility in the distribution of the ophthalmic division of the right trigeminal nerve was diminished. Lumbar puncture revealed normal hydrodynamics with normal cerebrospinal fluid. Roentgenograms of the skull showed destruction of the sella turcica and erosion of the walls of the sphenoidal sinus and clivus. Bilateral percutaneous carotid angiograms demonstrated occlusion of the right internal carotid artery. The petrous portion of the left internal carotid artery was constricted and the $A_1$ segments of both anterior cerebral arteries were elevated.

Course. During the first 24 hours of hospitalization he became comatose. Despite intensive sup portive therapy, he died 48 hours after admission.

Complete autopsy was performed. The pertinent findings were limited to the head. The brain weighed 1495 gm. A hemorrhagic, multicystic tumor was found which had destroyed the major part of the sella turcica, invading the sphenoidal sinus and the right cavernous sinus. The right internal carotid artery was occluded with thrombus; the tumor surrounded the artery and was adherent to the adventitia. The neural structures of the right cavernous sinus and of Meckel's cave were invaded by tumor. The hypothalamus was distorted and compressed, but not invaded by tumor. No metastatic deposits were found.

Microscopic Examination. The tumor was composed of diffuse sheets of cells lacking orderly arrangement. The cytoplasm was agranular, moderate in amount and stained uniformly with eosin. The nuclei were essentially monomorphic, ovoid, and possessed a delicate network of chromatin. Connective tissue was inconspicuous. Mitotic figures were observed only rarely. There was extension of tumor into the cavernous sinus, Meckel's cave and into the adventitia of the carotid artery. The deeper layers of the wall of the carotid artery were not invaded by tumor. The brain itself was compressed by tumor, but not invaded by it (Figs. 5 and 6). Diagnosis of invasive pituitary adenoma was made. Death was

Figs. 5 and 6. Case 4. Pituitary adenoma. (Left) Note invasion of gasserian ganglion by tumor cells. Hematoxylin and eosin, $\times 110$. (Right) Tumor cells are essentially monomorphic. Appearance of neoplastic cells is benign. Hematoxylin and eosin, $\times 630$. 
attributed to spontaneous bleeding into the neoplasm.

Case 5. An 18-year-old soldier was admitted March 29, 1963 complaining of bilateral frontotemporal headaches of 2 years' duration.

Of significance in the past history was a tendency toward obesity and galactorrhea, which had stopped spontaneously 18 months prior to admission.

Examination. The patient was a slightly obese young man with sparse hair on the body. Except for slight proptosis of his right eye, complete evaluation of the eyes was within normal limits. He had a very slight spastic left hemiparesis. Roentgenograms of the skull demonstrated extensive destruction of the sella turcica. A soft-tissue density was seen extending into the sphenoidal sinus. The apex of the right petrous bone and the right greater wing of the sphenoid bone were eroded. Laboratory studies, including tests of endocrinologic function, were all within normal limits. Bilateral percutaneous carotid angiograms demonstrated opening of both carotid sinuses; the A1 segments of both anterior cerebral arteries and the proximal parts of both middle cerebral arteries were displaced superiorly.

Operation. A right temporoparietal craniotomy was performed on May 2, 1963. An extensive, friable tumor, which bled easily, was seen to have involved the major portion of the floor of the right middle cranial fossa extending onto the sphenoidal ridge and surface of the temporal lobe. The bony structures, nerves and blood vessels were surrounded by tumor. A biopsy was taken.

Microscopic Examination. The tumor was composed of masses of cells that lacked orderly arrangement. The cytoplasm was agranular, amphophilic and was contained within well-defined cellular boundaries. The nuclei were pleomorphic, occasionally pyknotic, and sometimes multiple or lobulated. The pattern of chromatin varied from being delicate and net-like to appearing clumped. Many blood-filled spaces were present. Connective-tissue stroma and mitotic figures were inconspicuous. An occasional amorphous mineral deposit was seen. Blood vessels appeared normal. Diagnosis of invasive pituitary adenoma (Fig. 7) with cellular atypism was made.

Course. The patient's postoperative status remained the same as it was preoperatively, except for a mild weakness of the right lateral rectus muscle. The 2000 kv. unit was used to administer 6067 r to the tumor through 8 X 10 cm. right and left lateral ports in the skull and through a 150° vertex arc, dividing 32 treatments over 47 days, which he tolerated well.

During the year following his admission, he has remained mentally clear and active. He has been asymptomatic except for an occasional headache. His physical deficits consist of the previously noted weakness of the muscle of the right eye, and cerebrospinal-fluid rhinorrhea, which developed in September 1963.

In February 1964, 7 months after completion of

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Fig. 7. Case 5. Pituitary adenoma. Pleomorphism is prominent. Hematoxylin and eosin, X620.
radiation therapy, bilateral percutaneous carotid angiograms were repeated which were interpreted as showing a small, but definite shift of the displaced vessels toward their normal positions.

Discussion

There is no uniformity of opinion concerning the proper term to be used in describing these malignant tumors. Bailey and Cutler\(^4\) called them malignant adenomas, thereby setting them apart from the benign adenomas. In doing so, they used the criteria of rapid progression of symptoms, invasiveness, and a distinctive histologic appearance. Feiring et al.,\(^5\) however, preferred the term carcinoma to identify their 3 cases of adenohypophysial neoplasms, which were characterized by rapid growth, failure to respond to radiation therapy and a histologically anaplastic appearance. Wise et al.\(^6\) were of the opinion that adenohypophysial neoplasms which show gross or microscopic evidence of invasion should be considered carcinomas. The usual histologic parameters of malignancy (pleomorphism of cells and nuclei, multinucleated and giant cells, mitoses, cellular disarray) frequently fail to correlate with the ultimate malignant potentialities of adenohypophysial neoplasms. We observe this quite clearly in the reports of Cohen and Dible,\(^2\) Forbes,\(^4\) and Sheldon et al.\(^7\) which comprise 3 of the 5 reported instances of adenohypophysial neoplasm with distant blood-borne metastases. Each of them is a carcinoma by definition, but each presents a more benign histologic appearance than the majority of the nonmetastasizing invasive tumors reported here (Cases 1, 2, 3 and 5) and in the literature.\(^1,3,5,9,10\) Local invasiveness cannot be correlated well with the histology either, as exemplified by Case 4, and corroborated by Kernohan and Sayre's experience.\(^7\)

To recapitulate: Pituitary adenomas may be grossly malignant (invasive), but histologically benign; they may be grossly and histologically malignant, but metastasize rarely, or they may be grossly and histologically benign, but capable of metastasizing via the blood stream. We prefer to call those which locally invade contiguous structures, but do not metastasize, invasive pituitary adenoma. The term carcinoma is reserved for those tumors with blood-borne metastases.

Our patients serve to illustrate a number of features commonly observed in this tumor. For example, the age at the time of onset of significant symptoms tends to be somewhat lower in this group when compared with the usual noninvasive adenomas. A statistically valid conclusion cannot be drawn from such a small group; nevertheless, our experience coupled with that of others\(^7\) seems to support this assessment.

The duration of significant symptoms prior to the patient's seeking medical advice is quite variable. In our patients it varied from a few days to 18 months. The reason in part may be because an invasive pituitary adenoma seems to be able to involve nerves and blood vessels extensively without producing symptoms (Case 4), or functional impairment. King\(^8\) stressed the importance of facial pain in the recognition of invasive pituitary adenomas which have involved the branches of the trigeminal nerve. Our experience agrees with that of Feiring et al.\(^5\) with regard to the frequent lack of correlation between invasion and clinical manifestations.

The presenting signs often differ from those that are observed in patients with the usual noninvasive tumor. Bitemporal hemianopsia, a common sign of noninvasive adenomas, was detectable on admission in only 1 of our 5 patients. Two had homonymous cuts in the visual fields. One had normal visual fields and normal visual acuity despite evidence of an extensive growth.

The lack of correlation between degree of involvement and the clinical picture is evident not only with involved blood vessels and nerves, but seems equally true concerning function of the pituitary gland. Hypopituitarism was found in only 1 of our patients prior to treatment. Three others, who had extensive studies of endocrinologic function, revealed no evidence of hypopituitarism which could be attributable to the effects of the tumor alone. The remaining patient died a few days after admission, but
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had no clinical or historical evidence to suggest inadequate function of the pituitary gland. The lower incidence of hypopituitarism in patients with invasive adenomas when compared with the incidence of hypopituitarism in patients with the noninvasive pituitary adenomas may in part be secondary to the ability of the invasive adenoma to escape from the confines of the sella turcica, and thereby provide a decompressive effect which is denied the noninvasive adenoma.

Excessive production of adrenocorticotrophic substances has not been noted in any of our patients. Except for the patient reported by Haugen and Loken who had an invasive nonmetastasizing pituitary adenoma, which they termed a carcinoma, the syndrome of excessive adrenocorticosteroid production secondary to pituitary hypersecretion has been associated only with metastasizing adenohypophysial tumors.

Invasive pituitary adenomas may invade walls of blood vessels, but infiltration extends no deeper than the adventitial layer. We observed this in the patient described in Case 4, thus supporting the experience of others. Tumor may be associated with thrombosis of the involved vessel, however, and in Case 4 was diagnosed antemortem by carotid angiography.

Roentgenograms of the skull and contrast studies served to focus our attention on the perisellar region. The findings, however, whether from erosion of bone or displacement of vessels, were not distinctive. Pre-operatively, in 4 of our patients, the possibility of the tumor being a craniopharyngioma, chordoma or intracranial invasion by a nasopharyngeal carcinoma was strongly considered.

Marked erosion of the body and wings of the sphenoid bone by invasive pituitary adenoma helps to distinguish it from the noninvasive variety, which shows much less destruction and is more apt to enlarge rather than destroy the sella turcica. Pituitary carcinomas (as we define them) characteristically show either a normal sella turcica, or one only slightly enlarged. In the patient reported by Scholz et al. the sella turcica was decalcified, presumably as the result of the associated Cushing's syndrome, and the sphenoidal sinus was opacified. Sheldon et al. made no mention of the appearance of the roentgenograms of the skull. Bailey and Cutler, in reporting their 3 patients with malignant adenomas, described destruction limited to the sella turcica on roentgenograms in 2 of the 3. In the 3 patients of Feiring et al. with nonmetastasizing tumors, which they termed carcinomas, destruction was also limited to the sella turcica.

Summarizing our experience with the roentgenographic appearance of the skull in patients with invasive pituitary adenomas, we found that in 4 of 5 patients, destruction of the bone went beyond simple expansion of the sella turcica. The wings of the sphenoid bone and/or the petrous apices were frequently eroded by the tumor, which is contrary to the experience of others.

Invasive pituitary adenomas have a tendency to bleed either spontaneously (Cases 3 and 4) or postoperatively (Case 2). This feature, when present, is recognized readily at operation at which time the tumor is seen to be friable and vascular. The most prudent course often is to make no attempt to remove even the major portion of the tumor. We are in agreement with Jefferson and White and Warren and believe that attempted total surgical removal of extensive pituitary adenomas is, more often than not, too hazardous.

There is insufficient evidence to allow valid conclusions to be drawn about the effectiveness of radiation therapy and its ultimate influence on prognosis. Many reports failed to give the dose to the tumor and/or the time-dose relationship, making comparison of results impossible. In other reports, in which apparently adequate dosages were recorded, the effects of irradiation were disappointing; however, survival for more than 5 years is not unusual. The addition of supervoltage radiation is a new variable and may result in increased survival. Two of our patients, treated with the supervoltage units, have survived for more than
10 years. One patient had no identifiable tumor at autopsy (Case 1). We conclude from this that supervoltage radiation in the treatment of invasive pituitary adenomas may be more effective than one might surmise from a review of the literature, and that some invasive pituitary adenomas are radio-curable. Additional evidence which lends support to this contention is recorded in Case 5.

Summary and Conclusions

Five patients with invasive pituitary adenomas have been presented. The diverse clinical and pathological features of these tumors have been called to attention, and correlated with the reports of others.

Malignancy, as applied to adenohypophysial tumors, means different things to different people. We prefer to regard pituitary adenomas as either noninvasive, invasive (those that extend beyond their capsules and invade contiguous structures) or as frank carcinomas, which are characterized by their ability to metastasize via the blood stream.

Invasive pituitary adenomas tend to occur in a younger age group. Presenting symptoms are usually quite different from those that frequently are associated with noninvasive adenomas. They often invade nerves and blood vessels without producing clinical manifestations. The roentgenographic appearance often suggests that one is dealing with a chordoma, craniopharyngioma or nasopharyngeal carcinoma because of the extensive destruction of the sphenoid and petrous portion of the temporal bones.

Our experience indicates that some invasive pituitary adenomas are radio-curable with the supervoltage roentgen-ray unit.

The treatment of these tumors involves craniotomy aimed primarily at obtaining neoplastic tissue for histologic diagnosis, followed by supervoltage radiation therapy.

References