Carcinoma of the Pituitary Gland with Metastases to the Spinal Cord and Roots of the Cauda Equina

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PITUITARY tumors of a malignant nature are uncommon and, for the most part, rarely metastasize. While local invasive tendencies occur with both malignant and nonmalignant neoplasms of the chromophobe type, distant spread either by the blood stream or by the cerebrospinal-fluid channels occurs with extreme rarity. Metastatic deposits have been discovered in the liver and lungs in most of the reported cases with disseminated lesions. Implantation into the distant areas of the spinal canal has been reported in only 2 cases. It is the purpose of this communication to review briefly the available reports on metastatic carcinoma of the pituitary gland and to present 1 patient with spread of the tumor by means of the subarachnoid fluid to the roots of the cauda equina. The management of this patient treated by means of laminectomy, rhizotomy and radiation will be discussed.

Case Report

K.B., a 29-year-old man, was first seen in December, 1956 complaining of blurred vision in the temporal quadrants of both eyes which was associated with severe frontotemporal headache and a loss of his former vigor and libido. Intermittent headache of a similar nature had first occurred in 1949. These headaches were most intense in the morning. There was no visual complaint and he was admitted to the U. S. Naval Hospital in Bethesda in May, 1950 because of the persistence of these symptoms. The general physical and neurological findings were normal at that time. Visual fields using 8/330 objects were normal and visual acuity in both eyes was 20/20. Roentgenograms of the skull, however, disclosed an enlarged sella measuring 15.0 mm. in anteroposterior diameter and 13.0 mm. in depth. Spinal-fluid pressure was normal; total content of protein was 34 mg. per cent; sugar and chlorides were normal. It was felt that the patient's headaches were caused by a chromophobe adenoma of the pituitary gland and radiation in surprisingly minimal dosage was given to the gland, 260 r in 11 days. Headache decreased in intensity after therapy but tended to recur in a milder form.

Examination. The patient was moderately obese with a light beard and finely textured pale skin. Axillary and pubic hair was sparse. The only positive neurological finding was a gross bitemporal hemianopsia. The optic discs were of normal color and delineation. Roentgenograms of the skull now disclosed thinning of the dorum sellae. The clivoids were sharp and the pituitary fossa was abnormally wide and deep with suggestive erosive alterations in the floor.

Treatment. Radiation was repeated, a total of 2,000 r being delivered to both right and left temporal areas in air with a calculated 3,000 r depth dose to the pituitary gland.

Course. Visual fields prior to therapy confirmed the presence of a bitemporal hemianopic defect most severe in the superior quadrants, the left more than the right. Following therapy, visual acuity which had been 20/40 improved to 20/20 and the fields returned to nearly normal except for a slight residual deficit in the superior temporal sectors.

The patient was first admitted to the Long Island Jewish Hospital on Aug. 17, 1959 because of rapid visual failure, more intense on the left side, where in addition to a defect in the temporal field the nasal quadrants were severely contracted. Deterioration had become evident during the preceding month with pallor of the optic disc on the left now being apparent. Roentgenograms of the skull disclosed enlargement of the sella with demineralization of the floor and of the dorum. A lumbar pneumoencephalogram showed a soft-tissue mass emanating from the sella and projecting into the 3rd ventricle. Angiography revealed straightening of the carotid siphon and elevation of the anterior cerebral arteries in their first portion. Spinal fluid was faintly yellow. The protein content was normal. The electroencephalogram was normal as was the uptake of radioactive iodine.

Received for publication December 8, 1963.
FIG. 1. Section of chromophobe adenoma removed at initial surgical procedure. There were nests of cells, some arranged radially around vessels, with ovoid and normochromatic nuclei. The cytoplasm was nongranular and chromophobic. Hematoxylin and eosin, ×270.

Operation performed on Aug. 24, 1959 was complicated by excessive swelling of the right frontal lobe, the tip being amputated at the termination of the procedure. The tumor, which appeared a deeper red than the usual gross appearance of a chromophobe adenoma, was biopsied and partially removed with difficulty by means of suction and curettage.

Course. After a stormy postoperative course, the patient gradually improved, manifesting transient euphoria, forgetfulness, incontinence, disorientation and confusion. A slight paresis of the right upper limb persisted at discharge on Sept. 10, 1959 with mild apraxia of the right hand. The visual deficit was severe in the left eye but had improved appreciably on the right.

Histologic Report. Sections of the specimen removed at operation (Fig. 1) revealed nests of cells, some of which were arranged radially around vessels. The nuclei were ovoid and normochromatic. The cytoplasm contained neither eosinophilic nor basophilic granules and was chromophobic. A number of calciospherites were seen. This lesion had the histologic features of a chromophobe adenoma and was reported as such. Evaluation of any invasiveness was not possible from this specimen.

Course. After discharge, vision deteriorated further and fell from 20/25 in the right eye on Sept. 30, 1959 to 20/200 on Oct. 24, 1959 and finally to 20/300 on Oct. 28, 1959. Vision in the left eye was maintained at finger-counting at 6 in. with severe constriction of the visual fields. Optic atrophy became more apparent on the left. Pneumoencephalography was repeated and disclosed further extension of the extrasellar portion of the tumor upwards and anteriorly into the 3rd ventricle, encroaching on the foramen of Monro.

2nd Operation. On Dec. 2, 1959 the wound was reexplored. Adhesions were stripped from the right optic nerve and chiasm after removal of an additional portion of the right frontal lobe. The tumor was surprisingly firm and resisted dissection until a central area of softening with semicystic consistency lent itself to further evacuation by means of curette and suction. The left optic nerve was only poorly perceived through dense adhesions that could not be removed without danger to the adjacent carotid artery. It was felt that evacuation of the content of the tumor had been satisfactory and that the right optic nerve and chiasm had been well decompressed. A stainless-steel plate was inserted to cover the defect in the frontal area left after the initial exploration.

Course. The postoperative course was uncomplicated, the patient being maintained on steroids before and after surgery.

A third course of radiation was given, this time with the cobalt-60 unit and providing a total tumor dose of 4,000 r. Vision improved slowly in the right eye and in June, 1961 had levelled at 20/30. No useful return of function was observed on the left.

Histologic Report. This time scant fragments of tissue were available for examination. Some of them showed recognizable portions of anterior
lobe of the pituitary merging into nests of tumor cells which, although resembling those found in the first specimen, were much more pleomorphic (Fig. 2). Retrospective examination of this specimen still does not permit classification of the tumor as malignant since, in common with adenomas of other endocrine glands, pleomorphic cells are found frequently in benign pituitary adenomas.

Course. The patient returned to work as an electrical engineer, receiving therapy consisting of cortisone, thyroid and androgens. In June, 1962, after an episode of nausea with retching, he complained of low-back pain radiating down the right lower extremity and to a lesser extent on the left. Pain grew progressively more intense and he failed to respond to rest in bed, traction, the use of a body cast and a great variety of medication provided by his attending orthopedist. Sphincteric function was unimpaired.

He was hospitalized once again on Sept. 2, 1962. Neurological examination revealed the residual visual defect in the temporal quadrants of both eyes, severe on the left where the contracted field persisted. The patient was in intense pain, the lower part of the back was flat and rigid with loss of all mobility. There was 1 in. of mid-thigh atrophy on the right but no gross weakness. Lasègue’s sign was markedly positive bilaterally with hyperactive reflexes in both lower extremities. Plantar responses were in flexion and there were no sensory alterations. The diagnosis on admission included a midline discal herniation with compression of the cauda equina and neoplasm. Roentgenograms of the lumbar and dorsal spine were normal except for 2 silver clips in the canal. Lumbar myelography disclosed multiple defects with a total block at the level of the 1st lumbar interspace. A second large defect was defined at the level between the 4th and 5th lumbar vertebrae with several smaller bead-like lesions scattered among the roots of the cauda equina (Fig. 3). The diagnosis of multiple tumors of the cauda equina was made, the findings suggesting multiple implants. Spinal fluid contained 264 mg. per cent protein, 1 white cell and 179 red cells.

3rd Operation. On Sept. 5, 1962 an extensive laminectomy of the 1st, 2nd, 4th and 5th lumbar and the 12th dorsal vertebrae was performed. The diagnosis of multiple implants of tumor was confirmed. The major areas were decompressed and two nodules on the dorsal roots at the level of the 4th and 5th segments were removed with the filaments of nerves.

Course. There was partial relief of the intense radicular pain down the right lower extremity. Conventional therapy with radiation over a 2-week period provided a tumor dose of 1,200 r to the spine, following which he was discharged. At this time he showed a mild, diffuse paresis in the lower extremities with anesthesia over the lateral aspect of the right leg and thigh. Diffuse atrophy was now present in the thighs and calves bilaterally. Plantar responses remained flexor. The right ankle reflex was absent, and the others were of 2+ intensity. The patient still complained of pain in the back and of varying distress down both lower limbs, but not of the former intensity and

Fig. 2. Sections of specimen removed during second operation. Greater pleomorphism is noted among the nests of tumor cells. The tumor could not be classified as malignant at this time. Hematoxylin and eosin, X270.
FIG. 3. Lumbar myelogram showing multiple defects indicative of implants of tumor among roots of the cauda equina, confirmed at laminectomy (A, B). A complete block to the flow of Pantopaque is seen at the level of T12-L1 interspace with a second oval defect immediately below it (C). The two silver clips in the spinal canal have descended from the original site of craniotomy, apparently following the same pattern of descent as the neoplastic cells.

requiring much less medication for relief. He was ambulatory with a spinal brace and physiotherapy was being provided to overcome flexion contractures at the knees.

On May 22, 1963 visual acuity was recorded at 20/25 in the right eye and at 20/200 in the left. He did not complain of headache and remained mentally alert with no further evidence of deterioration either at the cerebral or spinal levels. Progressive improvement in motor power was maintained in his lower extremities.

Histologic report was as follows: "Sections reveal portions of the roots of the cauda equina with actual infiltration by tumor cells between the nerve fibers (Fig. 4A). Comparison with the previous specimens from this patient's pituitary tumor removed in 1959 reveals a marked similarity of the cells composing the present tumor to those in the fragments of tissue that was interpreted at that time as a chromphobe adenoma of the pituitary gland. There is, however, much more anaplasia in the new specimen as well as an increased number of mitoses. The tumor (Fig. 4B, C) is an epithelial neoplasm composed of closely packed, large cells with abundant amphophilic cytoplasm and large nuclei, varying from moderately chromatic to hyperchromatic and bizarre with moderate numbers of mitoses. The tumor has an abundant vascular supply. This is now a pituitary carcinoma metastatic to the roots of the cauda equina."

Course. The patient did well for the following year until September, 1963, when low-back pain recurred. On this occasion, he was treated with

Fig. 4. (A) Infiltration of roots of the cauda equina by neoplastic cells. Hematoxylin and eosin, X 24. (B) Cellular detail from tumor in A. X 132. (C) Higher magnification of same, X 346. The tumor consists of large epithelial cells with abundant amphophilic cytoplasm and large nuclei, varying from moderately chromatic to hyperchromatic and bizarre, with moderate numbers of mitoses and a very abundant vascular supply. This is now a pituitary carcinoma.
the cobalt-60 unit, a dose of 3,000 r being delivered to the entire lumbar and lower dorsal spine. Improvement of a significant degree followed therapy, which permitted the patient to carry on his usual activity with minimal ancillary medication.

Review of the Literature

While malignant tumors of the pituitary gland are uncommon, peripheral metastases are rare. Even less frequent is the seeding of the spinal canal by metastatic deposits. In reviewing the 338 cases in Cushing's series of pituitary adenomas, Henderson found 11 that could be regarded as true adenocarcinomas, representing only about 1 per cent of all pituitary tumors. Metastases were found in the liver in only 1 case of this group.

In the 134 cases reported by Davidoff and Feiring only 1 malignant adenoma was found in an 18-year-old man. Jefferson described 3 patients of a group of 131 with chromophobe adenoma of the pituitary gland which demonstrated histologic features compatible with malignancy. Of the 71 pituitary adenomas reviewed by Grant, not a single malignant tumor was recorded although in 3 fatal cases the adenoma was observed to have spread beyond the sella and involved adjacent structures. Four of the 93 chromophobe adenomas in the series of Newton et al. were regarded as primary carcinomas. Ten per cent of the entire group of pituitary chromophobe adenomas demonstrated extrasellar extensions. Bailey and Cutler reported on 3 malignant chromophobe tumors in a group of 84 tumors of the pituitary gland. Distant metastases were not recorded in any of the above cases. This is surprising in view of the locally invasive nature of such neoplasms, with extension into the cavernous sinus being one of the most frequent complications of the distressing patterns of growth. The lack of anatomic proximity to lymphatics may explain this phenomenon. In the few isolated reports of metastatic lesions to the viscera, implants of tumor were found in the liver in 10 cases. Meningeal implantation into the distant areas of the spinal canal is an extremely unusual occurrence, having been recorded on only two occasions.

Salassa et al. described a man 42 years of age with Cushing's syndrome who was known to have an enlarged eroded sella with a calcified mass to one side and visual disturbances. A radical resection of a chromophobe adenoma containing calcium was performed in August, 1958, resulting in improvement in his visual disturbances. Because of subsequent rapid visual failure, therapy with radiation (3,000 r) was given in January, 1954. Paresis of the right 3rd and the left 3rd and 4th cranial nerves was noted at that time. A course of therapy with cobalt-60 radiation was given in January, 1955, a tumor dose of 4,100 r. While his vision improved, in the spring of 1955 he complained of radicular pain in the right lower extremity with loss of weight and showed neurologic evidence of a lesion of the lumbosacral plexus on the right. At his death in September, 1955 postmortem examination revealed a malignant pituitary adenoma with metastases to the liver, the spinal cord and the roots of the cauda equina, the latter being implants of tumor. The tumor also extended locally around the optic nerves and chiasm and backwards into the posterior fossa. Sections of both the tumor in the pituitary fossa and the implants were similar, the lesion being a highly malignant chromophobe tumor with great variation in the size of nuclei, many of which were hyperchromatic. This was the only malignant tumor found in the 12 patients of the entire group of 122 patients with Cushing's syndrome who had tumors of the pituitary gland.

The patient reported by Cairns and Russell was a man 25 years old in whom the diagnosis of a metastatic pituitary adenoma was made postmortem. Peculiar cells had been discovered in the spinal fluid. The pia-arachnoid over the dorsal surface of the cord appeared "milky-rusty" and opaque. Frequent multinucleated cells identical with those of the primary tumor were found in the subarachnoid space. No surgical procedure had been performed.

Madonick et al. described a case of
Pituitary Carcinoma with Spinal Metastases

chromophobe adenoma of the pituitary gland with metastases of identical histologic structure in the subarachnoid spaces over the surface of the temporal and frontal cortex as well as over the medulla. Definite microscopic intracerebral infiltration by small collections of neoplastic cells was found in a few areas of the hypothalamus overlying the cisterna interchiasmatica. Discrete metastatic foci were found in the leptomeninges of the interpeduncular fossa, the tela choroidea of the 3rd ventricle and in the Virchow-Robin spaces situated in the cerebral peduncle and internal capsule.

Four patients with Cushing's syndrome and malignant chromophobe adenoma of the pituitary gland have been reported7-9 in whom hepatic metastases occurred, including 1 with local invasion of the cervical lymph nodes.19 Two cases of Cushing's syndrome with basophilic carcinoma of the pituitary gland with liver metastases were presented by Cohen and Dible6 and by Sheldon et al.29

Newton et al.17 presented a 56-year-old man with acromegaly; postmortem examination 1 day after craniotomy revealed a small discrete nodule of tumor attached to the meninges near the right hippocampal gyrus, compressing the hippocampus. The tumor invaded the cavernous sinus and the roots of the trigeminal nerve. These authors also described the postmortem findings in a 15-year-old boy with a chromophobe adenocarcinoma of the pituitary gland invading the midbrain, pons and cavernous sinus. Neoplastic cells were found in the 4th ventricle with involvement of the cerebellum, cranial nerves, leptomeninges and dura mater. Another patient, a 27-year-old woman with acromegaly, expired following surgical exploration. Necropsy disclosed a large malignant adenoma invading the ganglion of the 5th nerve with a metastatic nodule attached to the meninges near the hippocampal gyrus.

Cagnetto2 described a patient with acromegaly in whom nodular collections of neoplastic cells found in the spinal pia mater were similar to those in the tumor of the pituitary gland.

Feiring et al.8 presented a similar case of a woman of 32 who had a chromophobe adenoma with remission of visual deficit and symptoms of amenorrhea following operation on the pituitary gland. She died 4 years later with symptoms of Cushing's syndrome and at necropsy was found to have an invasive pituitary carcinoma with metastases to the anterior cranial fossa.

Scholz et al.19 indicated that all cases of pituitary carcinoma with extracranial metastases verified by postmortem examination have apparently been associated with Cushing's syndrome. The patient in the present report is alive 12 years after his initial symptomatology and roentgenographic confirmation of an enlarged sella. There is no evidence to suggest the presence of Cushing's syndrome at this time. In the 1 case of metastases to the liver in the report of Henderson,12 there was no reference to a metabolic disturbance of this nature. Cavallero4 reported an adenocarcinoma of the hypophysis with metastases to the liver in a 59-year-old man. The neurohypophysis was completely destroyed with partial involvement of the infundibulum and the tuber cinereum. No evidence of Cushing's syndrome was present.

The earliest such lesion was found in a child 7½ years of age. The tumor of the pituitary gland was described as a malignant chromophobe adenoma with invasion of blood vessels as observed in the initial biopsy.10 She expired 8 months after operation, at which time tumor identical with the surgical specimen was found infiltrating the superior sagittal sinus, the right frontal lobe and the dura mater underneath the optic chiasm. Both lungs contained scattered metastatic lesions as did the liver.

Without citing specific cases, Kraus15 referred to multiple metastatic nodules in the leptomeninges "even as far as the cauda equina" found in patients with carcinomatous adenomas. Extension of the tumor was also observed into the bulbous venae jugulares with metastases to the lungs and pleura.

Discussion

The semantic dispute regarding the proper
terminology centers about evidence of distant metastases needed for the appropriate designation of carcinoma. The liver appears to be the one consistent target found in the majority of cases to date. Breakdown of the capsule of the tumor with extension into adjacent structures is the more common route of invasion by local metastases and is an essential criterion for the designation of malignant adenoma as employed by Jefferson and King. The term "carcinoma" was reserved for those cases with evidence of distant metastases carried either from the cavernous sinus into the blood stream or from the site of the tumor into the spinal fluid and subdural spaces. Jefferson indicated that pituitary malignancy was of a type peculiar to the organ of its origin and did not obey the general rules applied to carcinoma and sarcoma elsewhere.

The chromophobe elements appear more likely to undergo malignant transformation than the highly specialized acidophilic and basophilic cells. The malignant tumors invade the dura mater and base of the skull, extend along the dural planes over the floor of the middle fossa and back into the posterior cranial fossa. Extension occurs into the foramina at the base of the skull, through the cavernous sinus into the gas- terian complex, often resulting in facial pain as one of the paramount symptoms of malignant invasion. Multiple cranial-nerve involvement was noted in 3 cases of the Cushing series, impinging on the trigeminal, facial and acoustic nerves with palsies of the optic through the hypoglossal nerves in 2 individuals.

Both benign and malignant neoplasms may expand rapidly with enlargement of the sella and erosion of adjacent structures by pressure. On roentgenographic examination bone eroded by pressure has a sharp cortical margin; bone invaded by tumor presents an irregular, mottled appearance. Unfortunately, this has been impossible to confirm clinically and there remains no definite manner in which to differentiate between the benign and malignant adenomas by such studies.

The metastatic behavior of the malignant tumors of the pituitary gland cannot be predicted or correlated well with the microscopic appearance of the tumor. Differentiation of massive benign adenomas from malignant tumors may be difficult on gross examination since both may have extensive ramifications into adjacent structures. The benign lesion usually remains within its capsule, spreads by displacement of structures into the middle or anterior cranial fossae, displacing the hypothalamus, 3rd ventricle, and frontal and temporal lobes. The lesion may project downwards into the sphenoid sinus and nasopharynx or laterally compressing the cavernous sinus. The malignant tumor bursts its capsule and destroys by invasion of adjacent structures, most often spreading into the cavernous sinus and roots of the trigeminal nerve. Access to the ventricular system or basal cisterns is of primary importance in the production of metastases. A relatively benign tumor that arises in or near these spaces will also be liable to seeding in proportion to accessibility and exuberance of growth. Mononuclear cells other than lymphocytes discovered in the spinal fluid should arouse suspicion.

The microscopic characteristics of malignancy in these tumors, aside from infiltrating growth, include a loss of the normal alveolar arrangement of the cells, evidence of anaplasia and the presence of unusually large hyperchromatic and pleomorphic cells with frequent mitoses. Since, however, all of these features may also be present in benign pituitary adenomas, the one infallible criterion of malignancy is distant metastases.

No information is available regarding the effect of radiation on the distant metastatic deposits of tumors of the pituitary gland. The apparent response of the patient in this report suggests that it should be included in the program of therapy if adequate confirmation of the nature of the lesion is available, either through appropriate cellular study of the spinal-fluid content or by means of biopsy. Rhizotomy may or may not be necessary under such circumstances. Should neoplastic cells be found in the spinal fluid in
the presence of a syndrome of compression of
the cord or cauda equina, a therapeutic trial
may be indicated before surgical exploration
and decompression.

Summary

The case of a 29-year-old man with a car
cinoma of the pituitary gland is presented in
whom metastases to the roots of the cauda
equina occurred by means of the spinal-fluid
pathways. This is the third documented case
to occur and indicates the extreme rarity of
this complication. A method of management
is proposed which is based on the possible
response of the distant deposits to therapy by
radiation. The literature concerning malign-
nancies of the pituitary gland and the pattern
dissemination is reviewed.

Addendum

The patient was last examined in Septem-
ber 1964. An organic mental syndrome had
developed with evidence of intracranial hy-
pertension and internal hydrocephalus as
confirmed by angiography. The pain in his
back had been controllable prior to this, as it
had been following his last course of roentgen-
ray therapy. Further treatment was refused.

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